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Patents Form 1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
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Gwent NP9 1RH

1. Your reference	000219 /GB
2. Patent application number *(The Patent Office will fill in this part)*	**0030304.0** 13 DEC 2000
3. Full name, address and postcode of the or of each applicant *(underline all surnames)*	Eli Lilly and Company Lilly Corporate Center Indianapolis Indiana 46285 USA
Patents ADP number *(if you know it)*	4289040002
If the applicant is a corporate body, give the country/state of its incorporation	
4. Title of invention	COMPOUNDS
5. Name of your agent *(if you have one)*	MARTIN ALEXANDER HAY
"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	13 QUEEN VICTORIA STREET MACCLESFIELD CHESHIRE SK11 6LP
Patents ADP number *(if you know it)*	~~4246577001~~ 7710858001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body* *See note (d))*	No

Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	114 ✓
Claim(s)	17 ✓ ✓ W
Abstract	1
Drawing(s)	0

10. If you are also filing any of the following, state how many against each item.

Priority documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	0
Request for preliminary examination and search *(Patents Form 9/77)*	0
Request for substantive examination *(Patents Form 10/77)*	0
Any other documents *(please specify)*	0

11. I/We request the grant of a patent on the basis of this application

Signature Mark A Hay Date: 12 Dec 2000

12. Name and daytime telephone number of person to contact in the United Kingdom — MARTIN A. HAY 01625 500057

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Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write you answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

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COMPOUNDS

This invention relates to compounds which are inhibitors of serine proteases and to pharmaceutical compositions thereof and their use in the treatment of the human or animal body.

The serine proteases are a group of proteolytic enzymes which have a common catalytic mechanism characterized by a particularly reactive Ser residue. Examples of serine proteases include trypsin, tryptase, chymotrypsin, elastase, thrombin, plasmin, kallikrein, Complement C1, acrosomal protease, lysosomal protease, cocoonase, α-lytic protease, protease A, protease B, serine carboxypeptidase II, subtilisin, urokinase, Factor VIIa, Factor IXa, and Factor Xa. The serine proteases have been investigated extensively over a period of several decades and the therapeutic value of inhibitors of serine proteases is well understood.

Serine protease inhibitors play a central role in the regulation of a wide variety of physiological process including coagulation, fibrinolysis, fertilization, development, malignancy, neuromuscular patterning and inflammation. It is well known that these compounds inhibit a variety of circulating proteases as well as proteases that are activated or released in tissue. It is also becoming clear that serine protease inhibitors inhibit critical cellular processes, such as adhesion, migration, free radical production and apoptosis. In addition, animal experiments indicate that intravenously administered serine protease inhibitors, variants or cells expressing serine protease inhibitors, provide a protective effect against tissue damage.

Serine protease inhibitors have also been predicted to have potential beneficial uses in the treatment of disease in a wide variety of clinical areas such as oncology, neurology, haematology, pulmonary medicine, immunology, inflammation and infectious disease.

In particular serine protease inhibitors may be beneficial in the treatment of thrombotic diseases, asthma, emphysema, cirrhosis, arthritis, carcinoma, melanoma, restenosis, atheroma, trauma, shock and reperfusion injury.

Thus for example an inhibitor of Factor Xa has value as a therapeutic agent as an anticoagulant, e.g. in the treatment and prevention of thrombotic disorders. The use of a Factor Xa inhibitor as an anticoagulant is desirable in view of the selectivity of its effect. Many clinically approved anticoagulants have been associated with adverse events owing to the non-specific nature of their effects on the coagulation cascade.

Also, there are well-known associations of α1 protease inhibitor deficiency with emphysema and cirrhosis and C1 esterase inhibitor deficiency with angioedema.

It has now been found that certain aromatic compounds carrying bulky lipophilic side chains are particularly effective as inhibitors of serine proteases, especially proteases with negatively charged P1 specificity pockets, and most especially the serine proteases thrombin, and most importantly Factor Xa. The Factor Xa inhibitors of this invention are potentially useful for the prophylaxis or treatment of thrombotic disorders such as amongst others venous thrombosis, pulmonary embolism, arterial thrombosis, myocardial ischaemia, myocardial infarction, and cerebral thrombosis. They potentially have benefit in the treatment of acute vessel closure associated with thrombolytic therapy and restenosis, e.g. after transluminal coronary angioplasty or bypass grafting of the coronary or peripheral arteries and in the maintenance of vascular access patency in long term hemodialysis patients.

Factor Xa inhibitors of this invention may, with benefit, form part of a combination therapy with an anticoagulant with a different mode of action or with a thrombolytic agent.

It has been reported in WO99/11658 and WO99/11657 that certain benzamidine and aminoisoquinoline derivatives carrying a bulky lipophilic side chain are excellent inhibitors of serine proteases. Unfortunately, it has since been found that benzamidine compounds of WO 99/11658 in general demonstrate poor oral bioavailability.

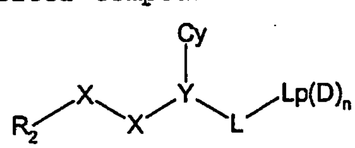
Surprisingly, it has now been found that certain other aromatic compounds also show inhibitory activity against

serine proteases, in particular Factor Xa, despite the lack of the amidino or 1-aminoisoquinoline functionality previously believed to be crucial for activity as a factor Xa inhibitor. Many of these compounds also possess other structural features that further distinguish them from the compounds of WO99/11658 and WO99/11657.

Where compounds of the invention have been tested, they have generally demonstrated superior oral bioavailability in comparison with benzamidines disclosed in WO 99/11658. Also, it has been found that the compounds of the invention perform excellently in the prothrombin time assay (PT) when compared to aminoisoquinolines of similar factor Xa activity and structure. The PT assay is a coagulation assay and it is widely accepted that direct acting Factor Xa inhibitors which perform well in the PT assay are more likely to be good antithrombotics.

In WO99/09053 certain 2-aminobenzamide compounds are disclosed as potential motilin receptor antagonists and in US 3268513 similar 2-aminobenzamide compounds are suggested as potential antibacterial agents. However, the novel compounds of the present invention have not before been suggested as potential serine protease inhibitors.

Thus viewed from one aspect the invention provides a serine protease inhibitor compound of formula (I)



(I)

wherein:

R_2 is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or R_1, or the substituents at the 3 and 4 positions taken together form a

fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R_2 cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_{1a} independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R_1 is as defined for R_{1a}, provided that R_1 is not unsubstituted aminoalkyl;

Y (the α-atom) is a nitrogen atom or a CR_{1b} group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, preferably containing 5 to 10 ring atoms and optionally substituted by groups R_{3a} or $R_{3i}X_i$;

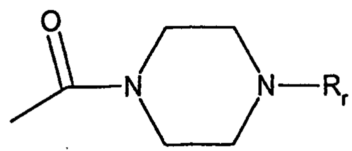
each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkyloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S; and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group), or $-OCH_2O-$ which is bonded to two adjacent ring atoms in Cy;

X_i is a bond, O, NH or CH_2;

R_{3i} is phenyl, pyridyl or pyrimidinyl optionally substituted by R_{3a};

R_{1b}, R_{1c} and R_{1j} are as defined for R_{1a}; and

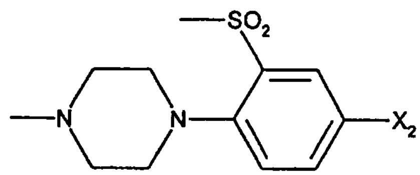
$-L-Lp(D)_n$ is of the formula:



in which R_r is $-(CH_2)_c-R_c$, $-CHR_eR_f$, $-CH_2-CHR_eR_f$, $-CH_2-CH_2-CHR_eR_f$, or R_g in which c is 1 or 2; R_c is thienyl, thiazolyl (which may bear an amino substituent), isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridyl (which may bear an alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, (1-4C)alkoxycarbonyl, carboxy, acetylamino, chloro, fluoro, cyano, (1-3C)alkyl, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl or tetrazolyl substituent), pyrimidinyl, pyridazinyl, pyrazinyl or phenyl (which may bear a methyl, methylamino, dimethylamino, carboxy, dialkylaminosulphonyl, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, alkoxycarbonyl, acetylamino, chloro, fluoro, cyano, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl or tetrazolyl substituent); each of R_e and R_f independently is hydrogen or C_{1-3}alkyl; or CHR_eR_f is cyclopentyl (which may bear a hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl substituent at the 3- or 4-position), cyclohexyl (which may bear a hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl substituent at the 3- or 4-position), tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, pyrrolidin-3-yl (which may bear a hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl substituent at the 1-position), piperidin-4-yl (which may bear a hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl substituent at the 1-position), or indan-2-yl; and R_g is 2-methylsulphonylphenyl which may bear a 4-fluoro substituent or R_g is λ^6-1,1-dioxobenzo[b]thiophen-7-yl;

or a physiologically-tolerable salt thereof (e.g. a halide, phosphate or sulfate salt or a salt with ammonium or

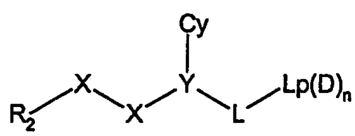
an organic amine such as ethylamine or meglumine); provided that Lp(D)n is not of the formula (K):



(K)

wherein X_2 is fluoro or hydrogen.

In another aspect the invention relates to a serine protease inhibitor compound of formula (I)



(I)

wherein:

R_2 is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or R_1, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R_2 cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_{1a} independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino,

acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R_1 is as defined for R_{1a}, provided that R_1 is not unsubstituted aminoalkyl;

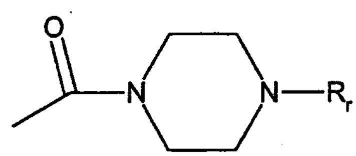
Y (the α-atom) is a nitrogen atom or a CR_{1b} group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, preferably containing 5 to 10 ring atoms and optionally substituted by groups R_{3a} or phenyl optionally substituted by R_{3a};

each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl;

R_{1b}, R_{1c} and R_{1j} are as defined for R_{1a};

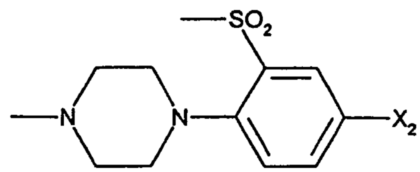
and -L-Lp(D)$_n$ is of the formula:



in which R_r is $-(CH_2)_c-R_c$, $-CHR_eR_f$, $-CH_2-CHR_eR_f$, or R_g in which c is 1 or 2; R_c is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, $CONH_2$, SO_2NH_2, methylaminosulphonyl, dimethylaminosulphonyl, methoxy or methylsulfonyl substituent); each of R_e and R_f independently is hydrogen or C_{1-3}alkyl; or CHR_eR_f is cyclopentyl (which may bear a methyl, ethyl or hydroxymethyl substituent at the 3- or 4-position), cyclohexyl (which may bear a methyl, ethyl or hydroxymethyl substituent at the 3- or 4-position), tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, pyrrolidin-3-yl (which may bear a 1-methyl substituent), piperidin-4-yl (which may bear a 1-methyl substituent), or indan-2-yl; and R_g is 2-methylsulphonylphenyl which may bear a 4-fluoro substituent or R_g is λ^6-1,1-dioxobenzo[b]thiophen-7-yl;

or a physiologically-tolerable salt thereof;

provided that Lp(D)n is not of the formula (K):



(K)

wherein X_2 is fluoro or hydrogen.

In the compounds of the invention, where the alpha atom is carbon it preferably has the conformation that would result from construction from a D-α-aminoacid NH_2-CR_{1b}(Cy)-COOH where the NH_2 represents part of X-X. Likewise the fourth substituent R_{1b} at an alpha carbon is preferably a methyl or hydroxymethyl group or hydrogen.

In the compounds of the invention, unless otherwise indicated, aryl groups preferably contain 5 to 10 ring atoms optionally including 1, 2 or 3 heteroatoms selected from O, N and S; alkyl, alkenyl or alkynyl groups or alkylene moieties preferably contain up to 6 carbons, e.g. C_{1-6} or C_{1-3}; cyclic groups preferably have ring sizes of 3 to 8 atoms; and fused multicyclic groups preferably contain 8 to 16 ring atoms.

Examples of particular values for R_{1a} are: hydrogen, methyl or ethyl. R_{1a} is preferably a hydrogen atom.

The linker group (X-X) from the R_2 group to the alpha atom is preferably selected from -CH=CH-, -CONH-, -$CONR_{1a}$-, -NH-CO-, -NH-CH_2-, -CH_2-NH-, -CH_2O-, -OCH_2-, -COO-, -OC=O- and -CH_2CH_2-. Preferably, the X moiety nearest to the alpha atom is an NH or O atom, most preferably a NH group. The X moiety alpha to the aromatic ring is preferably a carbon based group such as CH_2 or CO, preferably CO. Thus a particularly preferred linker X-X is -CONH-. In an alternative embodiment the linker is a -OCH_2- group.

Examples of particular values for R_{1b} are: hydrogen, (1-4C)alkyl, such as methyl or hydroxy(1-4C)alkyl, such as hydroxymethyl. R_{1b} is preferably a hydrogen atom.

The alpha atom (Y) is preferably a CH or C(CH_3) group. Especially the alpha atom (Y) is CH.

Examples of particular values for -CHR_eR_f in a -CHR_eR_f, -CH_2-CHR_eR_f or -CH_2-CH_2-CHR_eR_f group are 2-propyl, 3-pentyl, cyclopentyl, cyclohexyl, 4-methylcyclohexyl, tetrahydrothio-

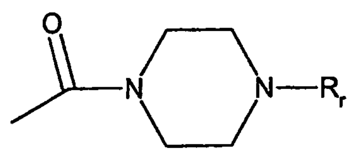
pyran-4-yl, pyrrolidin-3-yl, 1-methylpyrrolidin-3-yl, 1-(2-propyl)pyrrolidin-3-yl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-(2-propyl)piperidin-4-yl and indan-2-yl.

When Rr is of the formula $-CHR_eR_f$ a preferred value for Rr is 1-methylpiperidin-4-yl.

Preferably R_r is of the formula $-(CH_2)_c-R_c$.

Preferably c is 2.

Preferably $-L-Lp(D)_n$ is of the formula:



in which R_r is $-(CH_2)_c-R_c$; in which c is 2; R_c is thienyl, thiazolyl (which may bear an amino substituent), isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridyl (which may bear an amino, methoxycarbonyl, carboxy, fluoro, cyano, methyl, methylsulphonyl, aminosulphonyl, methylaminosulphonyl or dimethylaminosulphonyl or trifluoromethyl substituent), pyrimidinyl, pyridazinyl, pyrazinyl or phenyl (which phenyl may bear a fluoro, chloro, cyano, methyl, amino, methylsulphonyl, aminosulphonyl, methylaminosulphonyl, dimethylaminosulphonyl, methylamino, dimethylamino, carboxy, methoxycarbonyl or methoxy substituent).

Preferably, Rc is thiazolyl, (which may bear an amino substituent), pyrazolyl, imidazolyl, pyridyl (which may bear a methylsulphonyl, aminosulphonyl, methylaminosulphonyl, dimethylaminosulphonyl, fluoro, cyano, methyl or trifluoromethyl substituent), pyrimidinyl, pyridazinyl, pyrazinyl or phenyl (which phenyl may bear a fluoro, chloro, cyano, methyl, amino, methylamino, dimethylamino, carboxy, methoxycarbonyl, methylsulphonyl, aminosulphonyl, methylaminosulphonyl, dimethylaminosulphonyl or methoxy substituent).

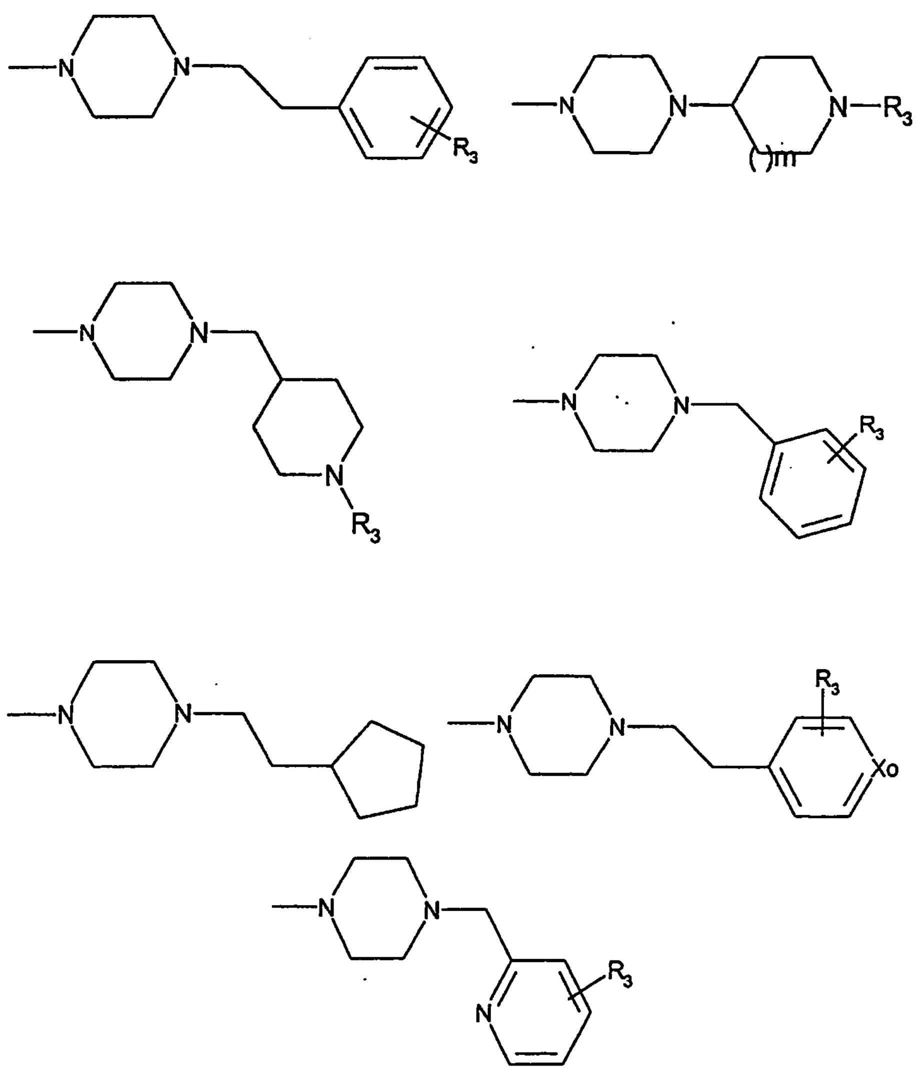
More preferably, Rc is thiazolyl (which may bear an amino substituent), pyrazolyl, imidazolyl, pyridyl (which may bear a fluoro, cyano, methyl or trifluoromethyl substituent), pyridazinyl or pyrazinyl.

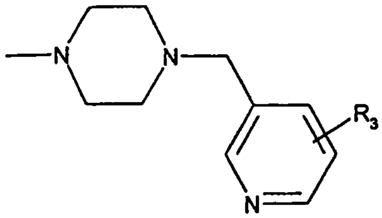
Yet more preferably Rc is thiazol-2-yl, 2-aminothiazol-4-yl, pyrazol-1-yl, pyrazol-4-yl, pyridazin-3-yl, imidazol-1-yl, imidazol-4-yl, pyrazin-2-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 3-fluoropyrid-4-yl, 2-cyanopyrid-4-yl, 2-methylpyrid-4-yl or 2-trifluoromethylpyrid-6-yl.

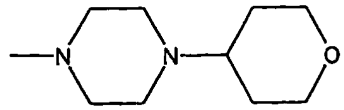
Yet more preferably, Rc is pyrazolyl, imidazolyl, pyridyl, pyridazinyl or pyrazinyl.

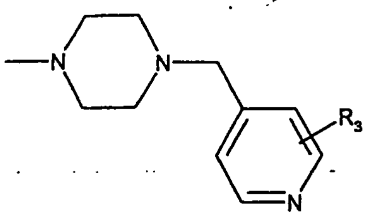
Preferably R_c is pyrid-2-yl, pyrid-3-yl or pyrid-4-yl.

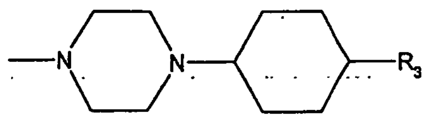
Most preferably, L is CO and the lipophilic group -Lp(D)n is selected from the formulae:

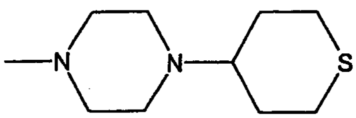


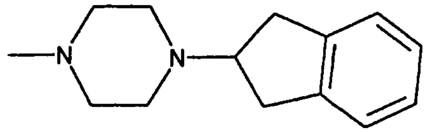


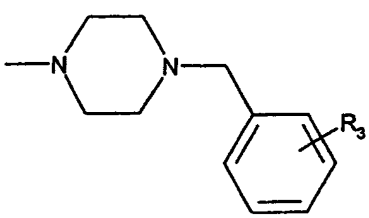


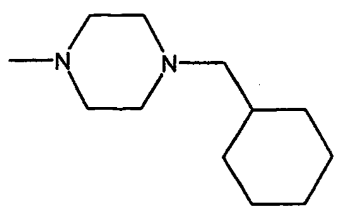


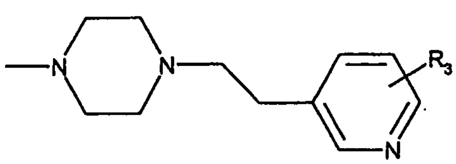


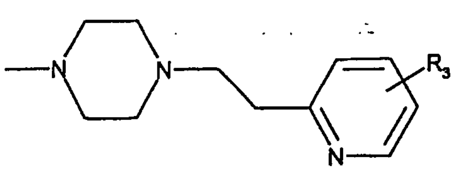


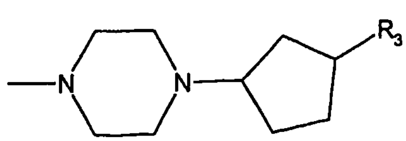












wherein;

m represents 0 or 1;

X^0 represents CH or N; and

R_3 is as defined for R3a.

Preferably m is 1.

Examples of particular values for R_3 are:-

hydrogen;

hydroxyl;

for alkoxy: methoxy or ethoxy;

for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkyl, such as methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, t-butyl, pentyl, 2-pentyl or 3- pentyl, (1-6C)alkylamino(1-6C)alkyl, such as isopropylaminomethyl, dimethylamino-methyl, diethylaminomethyl or dimethylaminoethyl, or (1-6C)alkanoyl, such as acetyl;

for hydroxyalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)hydroxyalkyl, such as hydroxymethyl or hydroxyethyl, carboxy or carboxy(1-5C)alkyl;

for alkoxyalkyl: methoxymethyl;

for alkoxycarbonyl: methoxycarbonyl or ethoxycarbonyl:

for alkylaminocarbonyl: methylaminocarbonyl or dimethylaminocarbonyl;

for aminoalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: aminomethyl, aminocarbonyl or aminocarbonyl(1-5C)alkyl;

for alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: methylamino, dimethylamino, ethylamino, formylamino or acetylamino;

amino;

for halo: fluoro or chloro;

cyano;

nitro;

thiol;

for alkylthio: methylthio;

for alkylsulphonyl: methylsulphonyl, ethylsulphonyl or isopropylsulphonyl;

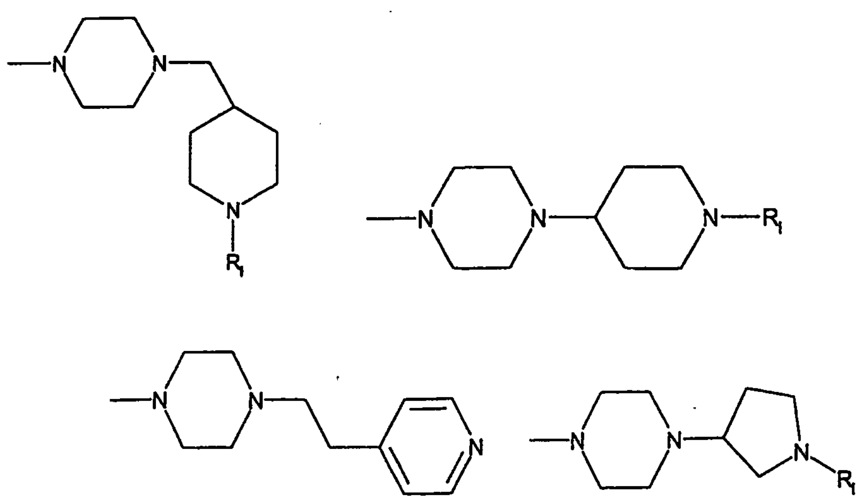
for alkylsulphenyl: methylsulphenyl (CH_3SO);

for triazolyl: 1,2,4-triazol-2-yl, 1,2,4-triazol-4-yl or 1,2,3-triazol-4-yl;
for imidazolyl: 1,3-imidazol-1-yl or 1,3-imidazol-4-yl;
for tetrazolyl: tetrazol-1-yl or tetrazol-5-yl;
for alkylsulphonamido: methylsulphonamido, ethylsulphonamido or propylsulphonamido;
for alkylaminosulphonyl: methylaminosulphonyl, ethylaminosulphonyl or propylaminosulphonyl;
aminosulphonyl;
for haloalkoxy: trifluoromethoxy; and
for haloalkyl: trifluoromethyl or trichloromethyl.

When R_3 is present as a substituent on an aromatic ring, it is preferably selected from hydrogen, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, alkoxycarbonyl, acetylamino, chloro, fluoro, cyano, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl and tetrazolyl.

When R_3 is present as a substituent on a saturated ring, it is preferably selected from hydrogen, hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl and ethoxycarbonyl.

For example specific Lp(D)n groups include



wherein R_1 is hydrogen or (1-6C)alkyl.
Preferably Ri is hydrogen, methyl or ethyl.

More preferably Ri is hydrogen or methyl.

The cyclic group (Cy) attached to the alpha carbon is preferably an optionally R_{3a} substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl, furanyl, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, imidazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrimidinyl, pyridazinyl, quinolyl, isoquinolyl, benzofuryl, benzothienyl or cycloalkyl group, or a phenyl group substituted by $R_{3i}X_i$ in which X_i is a bond, O, NH or CH_2 and R_{3i} is phenyl, pyridyl or pyrimidyl group optionally substituted by R_{3a}.

The cyclic group (Cy) attached to the alpha carbon is more preferably an optionally R_{3a} substituted phenyl, pyridyl (such as pyrid-2-yl, pyrid-3-yl or pyrid-4-yl), thienyl (such as thien-2-yl or thien-3-yl), thiazolyl (such as thiazol-2-yl, thiazol-4-yl or thiazol-5-yl), naphthyl (such as naphth-1-yl), piperidinyl (such as piperidin-4-yl) or cycloalkyl, such as a cyclohexyl group.

Examples of particular values for R_{3a} are:-

hydrogen;

hydroxyl;

for alkoxy: methoxy or ethoxy;

for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or ethyl, or alkylaminoalkyl, such as methylaminomethyl or dimethylaminomethyl;

for hydroxyalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: hydroxymethyl or carboxy;

for alkoxyalkyl: methoxymethyl;

for alkoxycarbonyl: methoxycarbonyl or ethoxycarbonyl;

for alkylaminocarbonyl: methylaminocarbonyl or dimethylaminocarbonyl;

for aminoalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: aminomethyl, $CONH_2$ or CH_2CONH_2;

for alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkanoylamino, such as acetylamino;

for alkoxycarbonylamino: methoxycarbonylaminno, ethoxycarbonylamino or t-butoxycarbonylamino;
amino;
for halo: fluoro or chloro;
cyano;
nitro;
thiol;
for alkylthio: methylthio;
for alkylsulphonyl: methylsulphonyl or ethylsulphonyl;
for alkylsulphenyl: methylsulphenyl;
for alkylsulphonamido: methylsulphonylamido or ethylsulphonylamido;
for alkylaminosulphonyl: methylaminosulphonyl or ethylaminosulphonyl;
aminosulphonyl;
for haloalkoxy: trifluoromethoxy;
for haloalkyl: trifluoromethyl;
for a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S and R^{11} and R^{12} are independently selected from hydrogen, methyl, ethyl, or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group: $-CONH_2$, -CONHMe, $-CON(Me)_2$, $-C(S)NH_2$, -C(S)NHMe, $-C(S)N(Me)_2$, pyrrolidin-1-ylcarbonylpiperidin-1-ylcarbonyl or morpholinocarbonyl; and
$-OCH_2O-$ which is bonded to two adjacent ring atoms in Cy.

In another aspect R_{3a} is selected from hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), aminoalkyl (substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl.

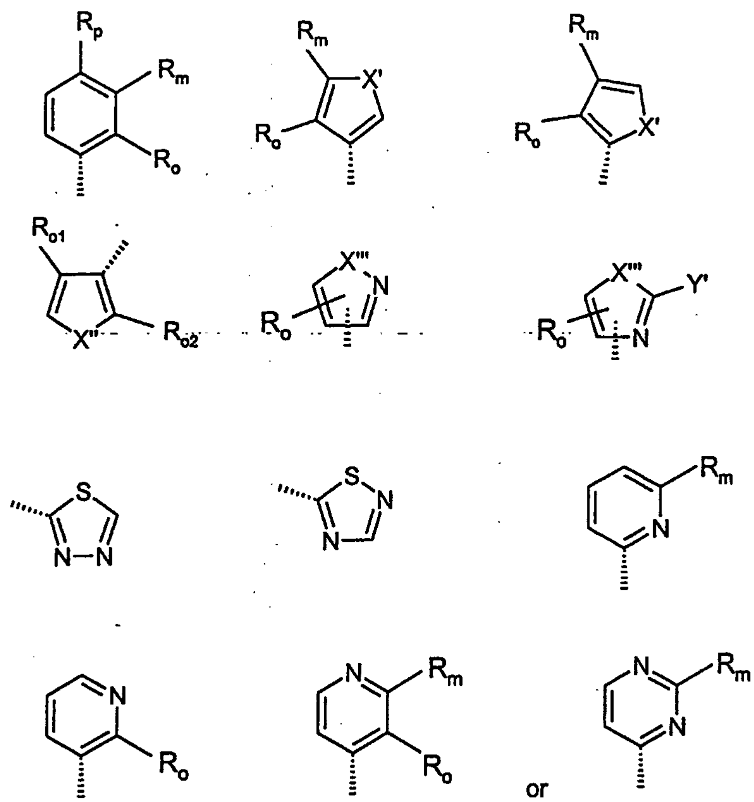
Preferably X^3 is O.

Examples of more specific values for R_{3a} include hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylamino-carbonyl, aminomethyl, $CONH_2$, CH_2CONH_2, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, bromo, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl, bromo, $-OCH_2O-$ (which is bonded to two adjacent ring atoms in Cy) and $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group).

More examples of specific values for R_{3a} include hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylamino-carbonyl, aminomethyl, $CONH_2$, CH_2CONH_2, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and trifluoromethyl.

Preferably R_{3a} is hydrogen, hydroxyl, methoxy, methyl, amino, fluoro, chloro, ethylsulphonylamino, amido or methylaminocarbonyl.

Preferably Cy is selected from:



wherein:

X' is selected from O, S and NMe;

X'' is selected from O and S;

X''' is selected from O, S, NH and NMe;

Y' is selected from hydrogen, amino and methyl;

R_o is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and methylsuphonyl;

R_m is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsuphonyl, carboxy, methoxycarbonyl and a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or

together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);
R_p is selected from hydrogen and fluoro; or
R_o and R_m or R_m and R_p form an $-OCH_2O-$ group; or
R_o and R_m together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroary ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sufur);
one of R_{o1} and R_{o2} is hydrogen and the other is R_o.

More preferably Cy is selected from phenyl (optionally substituted by methyl, ethyl, prop-2-yl, phenoxy, hydroxy, ethoxy, benzyloxy, prop-2-yloxy, nitro, amino, acetylamino, methylsulfonylamino, dimethylamino, chloro, methoxy, trifluoromethyl, methylthio, methylsulfonyl, tert-butylthio, tert-butylsulfonyl, aminosulfonyl or carbamoyl), pyridyl, thienyl, furanyl, imidazolyl, thiazolyl (optionally substituted by amino), napththyl, isoquinolinyl and quinolinyl.

Yet more preferably, Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5yl, naphthyl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl, and quinolin-8-yl.

Yet more preferably Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl and quinolin-4-yl.

Most preferably, Cy is selected from phenyl, 2-methoxyphenyl, 4-carbamoylphenyl and pyrid-2-yl.

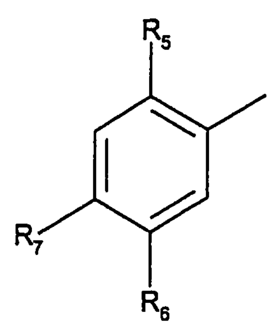
Most preferably Cy is phenyl.

Examples of particular values for R_{1C} are:
hydrogen;
hydroxyl;
for alkoxy: methoxy or ethoxy;
for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or

ethyl, or alkylaminoalkyl, such as methylaminomethyl or dimethylaminomethyl;
for hydroxyalkyl: hydroxymethyl;
for alkoxyalkyl: methoxymethyl;
for alkoxycarbonyl: methoxycabonyl or ethoxycarbonyl;
for alkylaminocarbonyl: methylaminocarbonyl or dimethylaminocarbonyl;
for alkoxycarbonylamino: methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino;
for alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkanoylamino, such as acetylamino; and
for aminoalkyl substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: aminomethyl, $CONH_2$ or CH_2CONH_2.

Referring to R^2, examples of a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom in R^2 are phenyl; pyrrolyl, such as 2-pyrrolyl; pyridyl, such as 3-pyridyl; pyrazinyl, such as 2-pyrazinyl; furyl, such as 2-furyl; and thienyl, such as 2-thienyl or 3-thienyl. Preferably the ring is interrupted (i.e. a carbon atom is replaced) by at most one heteroatom. In another aspect the ring is phenyl, 2-thienyl or 2-pyrrolyl. In yet another aspect, the ring is phenyl.

When the ring is phenyl, the group R_2 may be a group of formula



in which R_5 is amino, hydroxy or hydrogen, and R_6 and R_7 which may be the same or different represent halo, nitro, thiol, cyano, haloalkyl, haloalkoxy, amido, hydrazido, amino, alkylthio, alkenyl, alkynyl or R_1 or taken together form a 5 or 6 membered fused carbocyclic ring or 5 membered heterocyclic ring, which may itself be substituted by R_{1j},

amino, halo, cyano, nitro, thiol, alkylthio, haloalkyl, haloalkoxy.

When the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring, examples of the resultant bicyclic ring are naphthyl, such as 2-naphthyl; benzimidazolyl, such as benzimidazol-5-yl or benzimidazol-6-yl; isoquinolinyl, such as isoquinolin-7-yl; indolyl, such as indol-2-yl, indol-5-yl or indol-6-yl; indazolyl, such as indazol-5-yl; indazol-6-yl; 3,4-methylenedioxyphenyl; dihydroindolyl, such as 2,3-dihydroindol-6-yl; benzothiazolyl, such as benzothiazol-2-yl or benzothiazol-6-yl; benzo[b]thiophenyl, such as benzo[b]thiophen-2-yl; benzofuryl, such as benzofur-2-yl; imidazo[1,2-a]pyrimidinyl, such as imidazo[1,2-a]pyrimidin-2-yl; tetrahydroimidazo[1,2-a]pyrimidinyl, such as tetrahydroimidazo[1,2-a]pyrimidin-2-yl; and benzisoxazolyl, such as benzisoxazol-5-yl.

Preferably, R_2 is phenyl, thien-2-yl, naphthyl, indol-2-yl, indol-6-yl, benzo[b]furan-5-yl, benzo[b]thiophen-2-yl or benzimidazol-2-yl (each of which is optionally substituted as hereinabove defined).

It is preferred that at least one of R_6 and R_7 be other than hydrogen and that R_6, if present, is preferably a substituent containing one or more polar hydrogens such as hydroxy, amino, alkylamino, alkylaminoalkyl, aminocarbonyl, alkylaminocarbonyl, hydrazo and alkylhydrazo; alternatively R_6 and R_7 are joined together in the formation of a naphthyl or indolyl or azaindolyl or diazaindolyl group.

It is especially preferred that R_6 be amino and R_7 be chloro, bromo, methyl, methoxy or vinyl; or that R_6 and R_7 taken together form an indolyl ring with the NH at the 6-position or taken together form a naphthyl ring.

In another aspect R_2 represents:

(i) phenyl optionally being substituted in the 3 and/or 4 position by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or R_1, and optionally substituted at the 6 position by

amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio;

(ii) naphth-2-yl optionally substituted at the 6 or 7 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j} and optionally substituted at the 3 position by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio;

(iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl, indazol-5-yl, indazol-6-yl, benzothiazol-6-yl or benzisoxazol-5-yl optionally substituted at the 3 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j};

(iv) benzimidazol-5-yl or benzothiazol-6-yl optionally substituted at the 2 position by amino;

(v) thien-2-yl or thien-3-yl optionally substituted at the 4 or 5 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_1;

(vi) 3,4-methylenedioxyphenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

(vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

(viii) pyrazol-2-yl optionally substituted at the 5 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_1;

(ix) pyrid-2-yl optionally substituted at the 5 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_1;

(x) pyrid-3-yl optionally substituted at the 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_1;

(xi) benzofur-2-yl optionally substituted at the 3 position by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio and at the 5 or 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j};

(xii) indol-2-yl optionally substituted on the indole nitrogen atom by alkyl and optionally substituted at the 5 or

6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j};

(xiii) indol-6-yl substituted at the 5 position by amino, hydroxy, halo (such as fluoro or chloro), alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio and optionally substituted at the 3 position by halo (such as chloro), haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}; or

(xiv) benzo[b]thiophen-2-yl optionally substituted at the 3 position by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio and at the 5 or 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}.

Examples of particular values for substituents that may be present on R_2 are:

for halo: fluoro, chloro, bromo or iodo;
nitro;
thiol;
for haloalkoxy: difluoromethoxy or trifluoromethoxy;
hydrazido;
for alkylhydrazido: methylhydrazido;
amino;
cyano;
for haloalkyl: trifluoromethyl;
for alkylthio: methylthio;
for alkenyl: vinyl;
for alkynyl: ethynyl;
for acylamino: acetylamino;
carboxy;
for acyloxy: acetoxy;
hydroxy;
for alkyl: methyl or ethyl;
amido ($CONH_2$);
for aminoalkyl: aminomethyl; and
for alkoxy: methoxy or ethoxy.

Preferably R_2 is optionally substituted by 1 or 2 substituents selected from fluoro, chloro, amino, methyl, ethyl and methoxy.

Examples of particular values for R_1 are:

hydrogen;

hydroxy;

for alkoxy: methoxy or ethoxy;

for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or ethyl, alkylaminoalkyl, such as dimethylaminomethyl, or alkanoyl, such as acetyl;

for hydroxyalkyl: hydroxymethyl;

for alkoxyalkyl: methoxymethyl;

for alkoxycarbonyl: methoxycarbonyl;

for alkylaminocarbonyl: methylaminocarbonyl;

for alkylamino: methylamino, ethylamino or dimethylamino;

for hydroxyalkyl substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: carboxyl or carboxymethyl; and

for aminoalkyl substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: amido ($CONH_2$) or amidomethyl.

Examples of particular values for R_{1j} are:

hydrogen;

hydroxy;

for alkoxy: methoxy or ethoxy;

for alkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or ethyl, or alkanoyl, such as acetyl;

for hydroxyalkyl: hydroxymethyl;

for alkoxyalkyl: methoxymethyl;

for alkoxycarbonyl: methoxycarbonyl;

for alkylamino: methylamino, ethylamino or dimethylamino;

for hydroxyalkyl substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: carboxyl or carboxymethyl; and

for aminoalkyl substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: amido ($CONH_2$) or amidomethyl.

In yet another aspect R_2 represents:

(i) phenyl optionally being substituted in the 3 and/or 4 position by fluoro, chloro, bromo, iodo, nitro, difluoromethoxy, trifluoromethoxy, amino, cyano, trifluoromethyl, methylthio, vinyl, carboxy, acetoxy, $MeSO_2$-, hydroxy, methoxy, ethoxy, methyl, methoxycarbonyl,

methylamino, ethylamino or amido, and optionally substituted at the 6 position by amino, hydroxy, fluoro, methoxycarbonyl, cyano or aminomethyl (preferably phenyl substituted in the 4 position by chloro, amino, vinyl, methylamino, methyl or methoxy, optionally at the 3 position with amino or hydroxy, and optionally at the 6 position with amino or hydroxy);

(ii) naphth-2-yl optionally substituted at the 6, position by hydroxy and optionally substituted at the 3 position by amino or hydroxy;

(iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl, indazol-5-yl, indazol-6-yl, benzothiazol-6-yl or benzisoxazol-5-yl optionally substituted at the 3 position by chloro, bromo, amino, methyl or methoxy (preferably indol-6-yl optionally substituted at the 3 position by chloro, bromo, methyl or methoxy);

(iv) benzimidazol-5-yl or benzothiazol-6-yl optionally substituted at the 2 position by amino;

(v) thien-2-yl or thien-3-yl optionally substituted at the 4 or 5 position by methylthio, methyl or acetyl;

(vi) 3,4-methylenedioxyphenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

(vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

(viii) pyrazol-2-yl substituted at the 5 position by methyl;

(ix) pyrid-2-yl optionally substituted at the 6 position by chloro;

(x) pyrid-3-yl optionally substituted at the 4 position by chloro;

(xi) benzofur-2-yl optionally substituted at the 3 position by chloro, methyl or methoxy, at the 5 or 6 position by methyl and at the 6 position by methoxy;

(xii) indol-2-yl optionally substituted on the indole nitrogen atom by methyl and optionally substituted at the 5 or 6 position by fluoro, chloro, bromo, methyl or methoxy;

(xiii) indol-6-yl substituted at the 5 position by chloro, fluoro or hydroxy and optionally substituted at the 3 position by chloro or methyl; or

(xiv) benzo[b]thiophen-2-yl optionally substituted at the 3 position by fluoro, chloro or methyl, and optionally substituted at the 5 or 6 position by fluoro, chloro, methyl, hydroxy, or methoxy.

Particular values for R_2 are:

(i) phenyl, 2-aminophenyl, 3-aminophenyl, 2-amino-3-fluorophenyl, 2-amino-4-fluorophenyl, 2-amino-4-chlorophenyl, 2-amino-3-bromophenyl, 2-amino-3-nitrophenyl, 2-amino-4-nitrophenyl, 3,4-dimethoxy-5-aminophenyl, 2-amino-4-methylphenyl, 2-amino-3-methylphenyl, 2-amino-3-methoxyphenyl, 3,4-diaminophenyl, 3,5-diaminophenyl, 3-amino-4-fluorophenyl, 3-amino-4-chlorophenyl, 3-amino-4-bromophenyl, 3-amino-4-hydroxyphenyl, 3-amino-4-carboxymethylphenyl, 3-amino-4-methylphenyl, 3-amino-4-methoxyphenyl, 2-fluorophenyl, 4-fluoro-3-cyanophenyl, 3-chlorophenyl, 3-chloro-4-hydroxphenyl, 3-chloro-5-hydroxyphenyl, 4-chlorophenyl, 4-chloro-2-hydroxyphenyl, 4-chloro-3-hydroxyphenyl, 4-chloro-3-methylphenyl, 4-chloro-3-methoxyphenyl, 4-bromophenyl, 4-bromo-3-methylphenyl, 4-iodophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 3-cyano-5-aminophenyl, 2-hydroxphenyl, 2-hydroxy-4-methoxyphenyl, 3-hydroxphenyl, 3-hydroxy-4-methylphenyl, 2,4-dihydroxyphenyl, 3,4-dihydroxyphenyl, 3-hydroxy-4-methoxyphenyl, 4-difluoromethoxyphenyl, 4-trifluoromethoxphenyl, 4-trifluoromethylphenyl, 4-methylthiophenyl, 4-methoxycarbonylphenyl, 4-acetoxyphenyl, 4-methanesulfonylphenyl, 3-methylphenyl, 3-methyl-5-aminophenyl, 4-methylphenyl, 4-vinylphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-methoxy-3-chlorophenyl, 4-methoxy-3-methylphenyl, 3-methylaminophenyl, 4-methylaminophenyl, 4-ethylaminophenyl or 2-aminomethylphenyl;

(ii) naphth-2-yl, 3-aminonaphth-2-yl, 3-hydroxynaphth-2-yl or 6-hydroxynaphth-2-yl;

(iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl, 3-chloroindol-6-yl, 3-bromoindol-6-yl, 3-methylindol-6-yl, 3-methoxyindol-6-yl, indazol-5-yl, 3-aminoindazol-5-yl, indazol-6-yl, benzothiazol-6-yl, 3-aminobenzisoxazol-5-yl;

(iv) benzimidazol-5-yl, 2-aminobenzimidazol-5-yl, or benzothiazol-6-yl;

(v) thien-2-yl, 5-methylthien-2-yl, 5-methylthio-thien-2-yl, 5-acetylthien-2-yl or thien-3-yl;

(vi) 3,4-methylenedioxyphenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

(vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

(viii) 5-methylpyrazol-2-yl;

(ix) 5-chloropyrid-2-yl;

(x) pyrid-3-yl, 6-chloropyrid-3-yl;

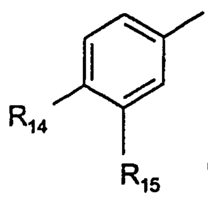
(xi) benzofur-2-yl, 5-chlorobenzofur-2-yl, 3-methylbenzofur-2-yl, 5-methylbenzofur-2-yl, 6-methoxybenzofur-2-yl;

(xii) indol-2-yl, 5-fluoroindol-2-yl, 5-chloroindol-2-yl, 5-methylindol-2-yl, 5-methoxindol-2-yl, 6-methoxyindol-2-yl and 1-methyl-indol-2-yl;

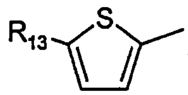
(xiii) 5-fluoroindol-6-yl; or

(xiv) benzo[b]thiophen-2-yl, 5-chloro- benzo[b]thiophen-2-yl or 6-chlorobenzo[b]thiophen-2-yl.

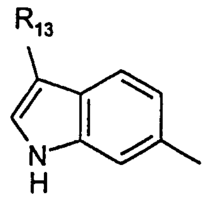
Preferably, R_2 is selected from one of the formulae (A') to (H'):



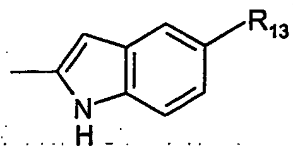
(A')



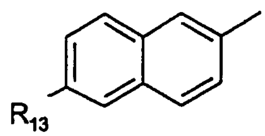
(B')



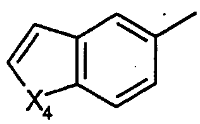
(C')



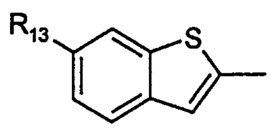
(D')



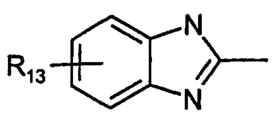
(E')



(F')



(G')



(H')

wherein X_4 is O or S, R_{13} is selected from hydrogen, fluoro [except for (C')], chloro or methyl and R_{14} is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and R_{15} is selected from hydrogen, methyl, fluoro, chloro and amino.

More preferably, R_2 is of the formula (A') (wherein R_{14} is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and R_{15} is selected from hydrogen, methyl, fluoro, chloro and amino) or of the formula (B') (wherein R_{13} is chloro) or of the formula (C') (wherein R_{13} is selected from hydrogen, methyl and chloro) or of the formula (D') (wherein R_{13} is selected from hydrogen, methyl, fluoro and chloro) or of the formula (E') (wherein R_{13} is hydrogen) or of the formula (G') (wherein R_{13} is chloro).

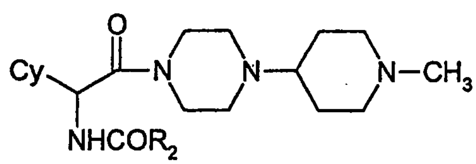
Yet more preferably, R_2 is 4-chlorophenyl, 4-methoxyphenyl, 3-amino-4-chlorophenyl, indol-2-yl, 5-

chloroindol-2-yl, indol-6-yl, 3-chloroindol-6-yl or 3-methylindol-6-yl.

Yet more preferably, R_2 is of the formula (A') or (C') and R_{13}, R_{14} and R_{15} are as defined hereinabove.

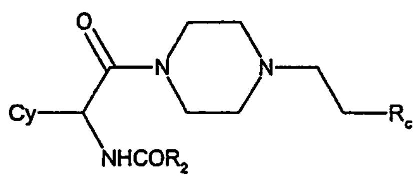
Most preferably, R_2 is of the formula (A') and R_{14} is methoxy and R_{15} is hydrogen or of the formula (C') and R_{13} is hydrogen, methyl or chloro.

Another preferred compound of the present invention is one of the formula:



wherein Cy and R_2 are as herinabove defined.

A preferred compound of the present invention is of the formula:



wherein Cy, R_2 and R_c are as hereinabove defined.

The compounds of the invention may be prepared by conventional chemical synthetic routes or by routes as illustrated by the following examples.

The compounds of the formula (I) may be prepared by forming the -X-X- bond from appropriate intermediates. For example, when -X-X- is -CONH- or -CO-NR$_{1a}$-, by reacting a compound of the formula (10): H_2N-Y-(Cy)-L-Lp(D)$_n$ with a compound of the formula R_2-COOH, under conditions known for the formation of an amide bond. The reaction is conveniently carried out in the presence of a benzotriazole-based reagent such as 1-hydroxybenzotriazole or 1-hydroxy-7-azabenzotriazole, in an inert organic solvent such as dimethylformamide and/or methylene chloride. The reaction mixture is usually taken to 0°C and then a dehydrating agent such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide added. Other suitable reagents and

solvents are known in the art, for example an acid halide, such as R_2-COCl.

Compounds wherein -X-X- is -NHCO- or -$NHCH_2$- may be formed from the appropriate intermediates using reaction conditions for the formation of an amide bond as described above and if necessary subsequent reduction of the resulting amide bond.

Compounds of the formula (I) wherein -X-X- is of the formula -CH_2NH- may be prepared by reducing the corresponding compound of the formula (I) wherein -X-X- is -CONH- or by reaction of a compound of formula (10): H_2N-Y-(Cy)-L-Lp(D)$_n$ with a compound of the formula R_2CHO and reducing the intermediate of the formula (I) wherein -X-X- is -C=N- with, for example, sodium cyanoborohydride.

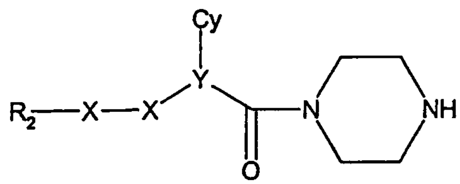
When -X-X- is -CH=CH-, the compounds of the formula (I) may be prepared using the Wittig or Horner-Emmons reactions. The corresponding compound in which -X-X- is -CH_2CH_2- can be formed by reduction of the -CH=CH- group, for example with hydrogen over a palladium-on-carbon catalyst.

An -X-X- bond of the formula -COO- or -OC(O)- may be formed by reacting the appropriate hydroxy and activated carboxylic acid (e.g. acid chloride or reactive ester) intermediates under conditions known for ester bond formation. Alternatively, a hydroxy and a carboxylic acid intermediate could be reacted together in the presence of diethylazodicarboxylate/triphenylphosphine.

An -X-X- bond of the formula -CH_2O- or -OCH_2- may be formed by reacting the appropriate hydroxy intermediate with the appropriate alkyl halide in the presence of a base. Conditions for the formation of an ether bond are known in the art.

These reactions can also be used to form intermediates, which contain one of the above -X-X- bonds.

Compounds of the formula (I) in which R_r is -$(CH_2)_c$-R_c may also be prepared by reductive coupling a compound of the formula (11):



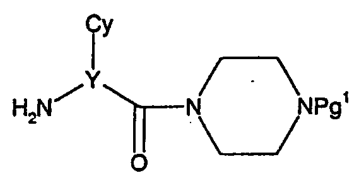
with a compound of formula (12)

$$OHC\text{-}(CH_2)_{c-1}\text{-}R_c$$

The reaction is conveniently performed in the presence of a reducing agent, such as sodium cyanobrohydride. Convenient solvents include alcohols, such as methanol, optionally with a halogenated hydrocarbon as solvent, such as 1,2-dichloroethane, and acetic acid. The coupling is conveniently effected at a temperature in the range of from 0 to 100°C.

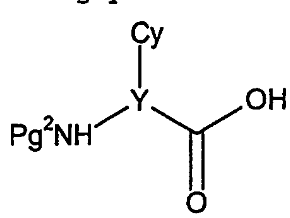
The intermediates of formula (11) are believed to be novel, and are provided as a further aspect of the invention.

The intermediates of formula (11) in which X-X is CONH may be prepared by reacting a compound of formula (13)

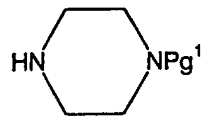


in which Pg^1 represents an amino protecting group, such as t-butoxycarbonyl, with a compound of formula R_2-COOH, under conditions known for the formation of an amide bond, for example as described hereinabove for forming a compound of formula (I), followed by deprotection.

The compounds of formula (13) may be prepared by reacting an appropriate N-protected glycine of formula (14)

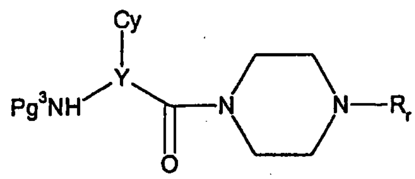


in which Pg^2 represents an amino protecting group that can be selectively removed in the presence of Pg^1 (for example, when Pg^1 is t-butoxycarbonyl, Pg^2 may be benzyloxycarbonyl), with a compound of formula (15)



under amide bond forming conditions, followed by selectively removing the protecting group Pg^2.

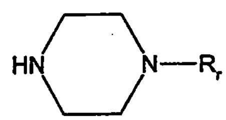
Compounds of the formula (10) in which X is CONH may be prepared by deprotecting a compound of the formula (16):



in which Pg^3 represents an amino protecting group, such as t-butoxycarbonyl.

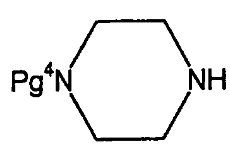
The intermediates of formula (16) and the corresponding amines without Pg^3 are believed to be novel, and are provided as a further aspect of the invention.

Compounds of formula (16) may be prepared by reacting a compound of formula (14) with a compound of formula (17)

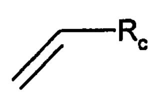


under amide bond forming conditions. The reaction is conveniently performed in the presence of diethylcyano-phosphate. Convenient solvents include amides, such as dimethylformamide. The temperature is conveniently in the range of from 0 to 100 °C.

Compounds of formula (17) in which R_r is $-(CH_2)_c-R_c$, may be prepared by reacting a compound of formula (18)



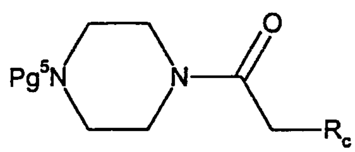
in which Pg^4 represents an amino protecting group, such as t-butoxycarbonyl, with a compound of formula (19)



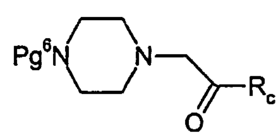
followed by removing the protecting group, Pg^4. The reaction

is conveniently performed in the presence of an acid, such as acetic acid. Convenient solvents include alcohols, such as ethanol.

Compounds of formula (17) in which R_r is $-(CH_2)_c-R_c$ may also be prepared by reducing compounds of formula (20) or formula (20A)



(20)



(20a)

in which Pg^5 and Pg^6 each represent an amino protecting group, such as t-butoxycarbonyl, followed by removing the protecting group, Pg^5. The reduction is conveniently performed in the presence of a reducing agent, such as borane, in an ether such as tetrahydrofuran.

Compounds of formula (20) may be prepared by reacting a compound of formula (18) with a compound of formula (21)

$$HOOC-(CH_2)_{c-1}-R_c$$

under amide bond forming conditions.

Alternatively, compounds of formula (20) may be prepared by reacting a compound of formula (18) with a compound of formula (21a)

$$HOOC-(CH)_{c-1}X'$$

(21a)

in which X' is a hydrogen atom, such as bromine, followed by reaction with a compound of formula (21b)

$$HR_c$$

in the presence of a strong base, such as sodium hydride.

Hence the present invention also provides a process for the preparation of a compound of formula (I) comprising:

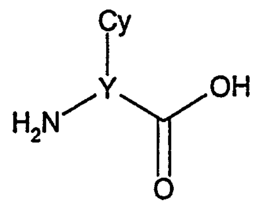
a) when -X-X is -CONH-, reacting a compound of formula (10) with a compound of formula R_2-COOH, under amide bond-forming conditions; or

b) when R_r is $-(CH_2)_c-R_c$, reacting a compound of formula (11) with a compound of (12);

wherein R_2, X, Y, Cy, c and R_r are as hereinabove defined and

formulae (10), (11) and (12) are as hereinabove defined, followed if a salt is required, by forming a physiologically acceptable salt.

An amino acid of formula (23)



or an N-protected glycine of formula (14) may be prepared (for example) by one or more of the following methods:

(i) from aryl or heteroaryl aldehydes via the Strecker synthesis or modifications thereof, via Bucherer-Bergs hydantoin synthesis, or via the Ugi methodology ("Isonitrile Chemistry", Ugi I. Ed.; Academic: New York, 1971;145-1999, ``Multicomponent Reactions with Isocyanides'', Domling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, 39, 3168; ``Amino Acid Derivatives by Multicomponent Reactions'', Dyker, G. *Angew, Chem. Int. Ed. Engl.* **1997**, 36, 1700; and also see ``A new Class of Convertible Isocyanides in the Ugi Four-Component Reaction'', Lindhorst, T.; Bock H.; Ugi, I. *Tetrahedron*, **1999**, 55, 7411.) with removal and replacement of protecting groups;

(ii) from styrenes via Sharpless methodology (J. Am. Chem. Soc. 1998,120, 1207-1217)

(iii) from aryl boronic acids via Petasis methodology (Tetrahedron, 1997, 53, 16463-16470) with removal and replacement of protecting groups;

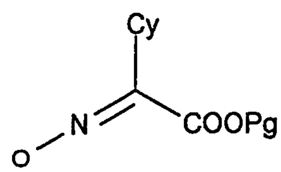
(iv) from aryl and heteroaryl acetic acids - via Evan's azidation (Synthesis, 1997, 536-540) or by oximation, followed by reduction and addition of protecting groups; or

(v) from existing aryl glycines by manipulation of functional groups, for example, alkylation of hydroxy groups, palladium assisted carbonylation of triflates derived from hydroxy groups and further manipulation of the carboxylic esters to give carboxylic acids by hydrolysis, carboxamides by activation of the carboxylic acid and coupling with amines,

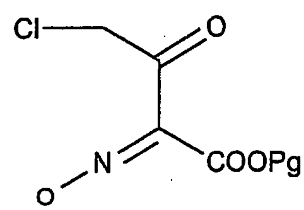
amines via Curtius reaction on the carboxylic acid;

(vi) from aliphatic, carbocylic and non-aromatic heterocyclic aldehydes and ketones using a Horner-Emmons reaction with N-benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester (Synthesis, 1992, 487-490); or

(vii) from oximes of formula



in which Pg is a carboxy protecting group, by reduction. (Oximes in which Cy is a heteroaryl group may be prepared from compounds of formula



Alternatively, oximes may be prepared by nitrosation of a compound of formula Cy-CH_2-COOPg, or by reaction of hydroxylamine with a compound of formula Cy-CO-COOPg).

A starting material for the preparation of a compound of formula (I), where the alpha atom is nitrogen, may be produced, for example, by reaction of a beta protected hydrazine (such protection to be chosen as to be compatible with the subsequent reagents to be employed) with phosgene, diphosgene, triphosgene or N,N'carbonyl diimidazole to give a reactive compound of the type PGNHN(Cy)COCl or PGNHN(Cy)CO-imidazole (wherein PG is a protecting group).

This intermediate may be used as has been described above for the carboxylic starting reagents where the alpha atom is carbon.

The skilled person will be aware that at certain stages in the synthesis of a compound of formula (I) it may be necessary to protect a reactive functional group in the

molecule to prevent unwanted side-reactions.

The protection of amino and carboxylic acid groups is described in McOmie, Protecting Groups in Organic Chemistry, Plenum Press, NY, 1973, and Greene and Wuts, Protecting Groups in Organic Synthesis, 2nd. Ed., John Wiley & Sons, NY, 1991. Examples of carboxy protecting groups include C_1-C_6 alkyl groups such as methyl, ethyl, *t*-butyl and *t*-amyl; aryl(C_1-C_4)alkyl groups such as benzyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, benzhydryl and trityl; silyl groups such as trimethylsilyl and t-butyldimethylsilyl; and allyl groups such as allyl and 1-(trimethylsilylmethyl)prop-1-en-3-yl.

Examples of amine protecting groups (PG) include acyl groups, such as groups of formula RCO in which R represents C_{1-6} alkyl, C_{3-10} cycloalkyl, phenyl C_{1-6} alkyl, phenyl, C_{1-6} alkoxy, phenyl C_{1-6} alkoxy, or a C_{3-10} cycloalkoxy, wherein a phenyl group may be optionally substituted, for example by one or two of halogen, C_1-C_4 alkyl and C_1-C_4 alkoxy.

Preferred amino protecting groups include benzyloxycarbonyl (CBz), t-butoxycarbonyl (Boc) and benzyl.

In another aspect the invention relates to a process for preparing a compound of formula I comprising deprotecting a compound of formula (I'):

$$R^{2'}\text{-X-X-Y(Cy')-L-Lp(D)}_n' \qquad \text{(I)}'$$

Wherein $R^{2'}$ is R^2 (as hereinabove defined) or protected R^2, Cy' is Cy (as hereinabove defined) or protected Cy and $Lp(D)_n'$ is $Lp(D)_n$ (as hereinabove defined) or protected $Lp(D)_n$; providing at least one protecting group is present.

If necessary physiologically tolerable salts can be formed using methods known in the art.

All novel intermediates described herein are provided as further aspects of the invention.

The compounds of the invention may be administered by any convenient route, e.g. into the gastrointestinal tract (e.g. rectally or orally), the nose, lungs, musculature or

vasculature or transdermally. The compounds may be administered in any convenient administrative form, e.g. tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g. diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents. Preferably the compositions will be sterile and in a solution or suspension form suitable for injection or infusion. Such compositions form a further aspect of the invention.

The following are examples of pharmaceutical compositions of compounds according to the invention.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active Ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

Tablets each containing 60 mg of active ingredient are made as follows:

Active Ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Viewed from this aspect the invention provides a pharmaceutical composition comprising a serine protease inhibitor according to the invention together with at least one pharmaceutically acceptable carrier or excipient. The pharmaceutical composition may also optionally comprise at least one further antithrombotic and/or thrombolytic agent.

Viewed from a further aspect the invention provides the use of a serine protease inhibitor according to the invention for the manufacture of a medicament for use in a method of treatment of the human or non-human animal body (e.g. a

mammalian, avian or reptilian body) to combat (i.e. treat or prevent) a condition responsive to said inhibitor.

Viewed from a further aspect the invention provides a method of treatment of the human or non-human animal body (e.g. a mammalian, avian or reptilian body) to combat a condition responsive to a serine protease inhibitor (e.g. a condition such as a thrombotic disorder responsive to a factor Xa inhibitor), said method comprising administering to said body an effective amount of a serine protease inhibitor according to the invention.

The dosage of the inhibitor compound of the invention will depend upon the nature and severity of the condition being treated, the administration route and the size and species of the patient. However in general, quantities of from 0.01 to 100 μmol/kg bodyweight will be administered.

All publications referred to herein are hereby incorporated by reference.

The invention will now be described further with reference to the following non-limiting Examples.

Experimental

The following abbreviations are used throughout: Boc (tertiary butyloxycarbonyl), CMA (chloroform: methanol, concentrated ammonium hydroxide 80:18:2), DCC (1,3-dicyclohexylcarbodiimide), DCM (dichloromethane), DEPC (diethyl cyanophosphonate), DIPEA (diisopropylethylamine), DMF (dimethylformamide), DMSO (dimethyl sulfoxide, perdeuterated if for NMR), EDCI (1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride), EtOAc (ethyl acetate), EtOH (ethanol), HATU ([O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate]), HOAt (1-hydroxy-7-azabenzotriazole), HOBT (1-hydroxy-benzotriazole), HPLC (high-performance liquid chromatography), IS-MS (ion spray mass spectrum), RPHPLC (reverse phase high-performance liquid chromatography), SCX (strong cation exchange resin), TFA (trifluoroacetic acid), THF (tetrahydrofuran), TLC (thin layer chromatography with R_f as relative mobility) .

All solution concentrations are expressed as %Vol./%Vol. unless otherwise stated. Reagents were obtained from a variety of commercial sources.

IR means an infrared spectrum was obtained. ^{1}NMR, 1H-NMR, or 1H NMR means a proton magnetic resonance spectrum was obtained.

HPLC Analysis

(Method A): Vydac C18 (4.6 x 250 mm), elute with a linear gradient of 90/10 through 50/50 (0.1% TFA in water / 0.1% TFA in acetonitrile) over 40 min, 1 mL/min.

(Method B): Waters Symmetry, C18 (4.6 x 250 mm) column. The elution system consisted of linear gradient from 95:5 (0.2% TFA in H_2O)/(0.2% TFA in CH_3CN) to 5:95 (0.2% TFA in H_2O)/ (0.2% TFA in CH_3CN) over 20 min, followed by (0.2% TFA in CH_3CN) isocratic over 15 min. The flow rate was 1 ml/min. UV

Detection was performed at 254 nm unless otherwise noted.

(Method C): Shimadzu LC6 gradient system equipped with an autosampler, a variable wavelength detector at flow rates of 0.4 ml/ min. Eluant A consisted of aqTFA (0.1%) and eluant B 90% MeCN in aq TFA(0.1%) with gradient elution (0 min. 20%B then 20% to 100% over 15 min.); Luna C18 (2.1x150 mm, 5μM particle size).

(Method D): Microsorb-MV C18 (4.6 x 250 mm) column. The elution system consisted of a linear gradient from 90:10 (2.5% TFA in H_2O):(2.5% TFA in acetonitrile) to 10:90 (2.5% TFA in H_2O):(2.5% TFA in acetonitrile) over 25 min at 30 °C and a flow rate of 1 mL/min. UV Detection was performed at 254 nm unless otherwise noted.

API-MS (atmospheric pressure chemical ionization mass spectra) were obtained on a PESciex API 150EX with a heated nebulizer and nitrogen as the reagent gas in positive ion mode.

CI-MS (Chemical ionization mass spectra) were obtained on a Shimadzu 5000 direct insertion mass spectrometer in chemical ionization mode utilizing methane as the reagent gas.

MALDI-TOF, Matrix assisted laser desorption ionisation - time of flight mass spectrometry, RT, retention time.

In general in this specification, "D-" or "R-" in the name of a product indicates the product was made beginning with a chiral starting material, for example D-phenylglycine.

Preparation of Starting Materials and Intermediates

Intermediate substituted glycine compounds for starting materials and intermediates, including those in which the amino group and/or the carboxy group is protected, conveniently may be prepared using one of the procedures below, or by a similar procedure. It may be convenient or

preferred to change the order of steps in the preparation of a compound of the invention and to use a similar procedure with a different intermediate. In particular, it may be convenient to use an acyl group R_2-CO- initially in a preparation, rather than an amino protecting group.

Abbreviations, in addition to others listed herein, include: TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical; (DHQD)2PHAL: hydroquinidine 1,4-phthalazinediyl diether; r.b., round bottomed;

Preparation of Intermediates KE-1 - KE-3

The following compounds were prepared according to the indicated method (Method KE-A) from the indicated starting materials, unless otherwise described.

Intermediate KE-1

Ethyl oxo-quinolin-8-yl-acetate.

Method KE-A

To a stirring solution of 8-bromoquinoline (10.1 g, 48.5 mmol) in THF (500 mL) at -78 °C was added dropwise a 1.3 M solution of sec-butyl lithium (37.3 mL, 48.5 mmol)in cyclohexane. After 5 min, diethyl oxalate (8 mL, 58.3 mmol) was added; and the solution was allowed to slowly warm to room temperature overnight. The next morning, the reaction was quenched with the addition of saturated aqueous NH_4Cl; and the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and satd aq. $NaHCO_3$; the layers were separated; and then the aqueous phase was washed with brine, dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed over silica gel, eluting with 20% ethyl acetate/hexanes through 25% ethyl acetate/hexanes. The product containing fractions were combined and concentrated in vacuo to give 5.88 g (53%) of the title compound.

1H-NMR

IS-MS, m/e 230.1 (M+1)

Intermediate KE-2

Ethyl oxo-quinolin-5-yl-acetate.

Prepared from 5-bromoquinoline and diethyl oxalate using Method KE-A.

1H-NMR
IS-MS, m/e 230.0 (M+1)

Intermediate KE-3

Ethyl oxo-thiazol-5-ylacetate.

To a r.b. flask (500 cm^3) under argon, fitted with ethanol thermometer, septum cap, and dropping funnel, was added anhydrous ether (100 cm^3) with stirring. This was cooled to -78C and 2M n-butyllithium (60 cm^3, 120 mmol) was added.

A solution of silyl thiazole (16g, 16cm^3, 100 mmol) in anhydrous ether (100 cm^3) was then added by dropping funnel over 30 minutes. This was allowed to stir for 1 hour to give a peach suspension. To this, was added diethyl oxalate (16.3 cm^3, 17.5g, 120 mmol) rapidly to give a brown solution, resulting in a temperature increase to -30 °C. This was allowed to cool back to -78 °C and stirred for 30 minutes. Reaction monitored by ^{1}H NMR ($CDCl_3$).

The brown solution was poured onto 5% hydrochloric acid solution (300 cm^3) with vigorous stirring for 30 minutes. Ether layer was separated and washed with saturated bicarbonate (*ca.* 80 cm^3), dried over magnesium sulphate, and concentrated *in vacuo* to give an orange oil. This was purified by flash chromatography (10% ethyl acetate/hexane) to give a yellow oil (7.31g, 39.47 mmol) [40% Yield].

^{1}H NMR ($CDCl_3$); 1.42 (3H, t), 4.45 (2H, q), 8.89 (1H, s), 9.10 (1H, s).

Preparation of Intermediates OX-1 - OX-7

The following compounds were prepared according to the indicated method (Method OX-A or Method OX-B) from the indicated

starting materials unless otherwise described.

Intermediate OX-1

Ethyl Hydroxyimino-pyridin-2-yl-acetate.

Method OX-A

To a stirring solution of ethyl 2-pyridylacetate (12.6 g, 76.3 mmol) in acetic acid (19 mL) at 5 °C was added a solution of sodium nitrite (6.05 g, 87.7 mmol) in water (12 mL) at a rate sufficient to maintain the internal temperature below 15 °C. After complete addition and an additional 30 min, an additional 30 mL of water were added. The resulting white precipitate was filtered, washed with water, satd aq. $NaHCO_3$, and again with water. The solid was then dried under vacuum to give 14.1 g (95%) of the title compound.

1H-NMR

IS-MS, m/e 194.9 (M+1)

Analysis for $C_9H_{10}N_2O_3$:

	Calcd:	C, 55.67; H, 5.19; N, 14.43;
	Found:	C, 55.79; H, 5.14; N, 14.13.

Intermediate OX-2

Ethyl Hydroxyimino-pyridin-3-yl-acetate.

Using the procedure of Tikk et al [Acta. Chimica, Hungarica, 114(3-4), 355], a mixture of ethyl hydroxyimino-pyridin-3-yl-acetate and n-butyl hydroxyimino-pyridin-3-yl-acetate was prepared from ethyl 3-pyridinyl-acetate and n-butyl nitrite.

1H-NMR

IS-MS, m/e 195 (M+1), 223.1 (M+1)

Intermediate OX-3

Ethyl Hydroxyimino-quinolin-8-yl-acetate.

Method OX-B

To a stirring solution of ethyl oxo-quinolin-8-yl-acetate

(5.5 g, 24 mmol) in ethanol (140 mL) was added sodium acetate (2.16 g, 26.4 mmol) followed by hydroxylamine hydrochloride (2.67 g, 38.4 mmol). The mixture was heated to reflux; and, after 7 h, the heating mantle was removed and the solution was allowed to stir overnight at room temperature. The next morning, the solvent was removed in vacuo and the residue was partitioned between ethyl acetate and satd aq. $NaHCO_3$. The layers were separated and the organic phase was washed with brine, dried with Na_2SO_4, filtered and concentrated in vacuo. The resulting foam was recrystalized from dichloromethane/hexanes to give an initial crop of 2.5 g of the title compound as an off-white solid, followed by 0.31 g of a second crop. The mother liquor was then concentrated in vacuo, the residue was dissolved in a minimal amount of dichloromethane. The solution was then chromatographed over silica gel, eluting with 30% ethyl acetate/hexanes, then 40% ethyl acetate/hexanes, and finally with ethyl acetate. The product containing fractions were combined and concentrated in vacuo to give 1.94 g of the title compound for a combined yield of 4.75 g (81%).

1H-NMR
IS-MS, m/e 245.0 (M+1)

Intermediate OX-4

Ethyl Hydroxyimino-quinolin-5-yl-acetate.

Prepared from ethyl oxo-quinolin-5-yl-acetate using Method OX-B.

1H-NMR
IS-MS, m/e 245.0 (M+1)

Intermediate OX-5

Ethyl Hydroxyimino-thiazol-5-ylacetate.

To a r.b. flask (500 cm^3) was added the ethyl oxo-thiazol-5-ylacetate (6.30g, 34.02 mmol) to ethanol (*ca.* 180 cm^3) with stirring. Sodium acetate (3.06g, 37.30 mmol) and

hydroxylamine hydrochloride (3.78g, 54.43 mmol) were then added to give an off-white suspension. This was brought to reflux at 85C for 1 hour. Reaction monitored by TLC (60% hexane/ethyl acetate; s.m. r.f 0.5, prod. r.f. 0.3.). Reaction cooled and concentrated *in vacuo*. Product taken up in ethyl acetate (*c.a.* 200 cm^3) and washed with 5% hydrochloric acid solution. Ethyl acetate layer was dried over magnesium sulphate and evaporated to dryness to give a cream solid (6.372g, 31.825 mmol) [94% Yield].

^1H NMR ($CDCl_3$); 1.40 (3H, m), 4.40 (2H, m), 8.06 ($^1/_3$H, s), 8.78 ($^1/_3$H, s), 8.95 ($^2/_3$H, s), 8.98 ($^2/_3$H,s).

Intermediate OX-6

Ethyl α-Oximino-thiazole-4-acetate.

To a 2 necked r.b. flask (100 cm^3) with ethanol thermometer, concentrated sulphuric acid (25 cm^3) was added and cooled to 0 °C with stirring. To this solution was added the ethyl-α-oximino-2-aminothiazole-4-acetate (5.00g, 23.231 mmol). Water (10 cm^3) was then added and cooled to -10 °C. A solution of sodium nitrite (1.683g, 24.393 mmol) in water (5 cm^3) was then added slowly over an hour keeping the temperature below -5°C.

To a separate r.b. flask (500 cm^3), water (180 cm^3) was added and cooled to 3°C. The reaction solution was poured in to the cold water with stirring and then cooled to -5°C. To this solution, 50% hypophosphoric acid (90 cm^3) was added dropwise over 10 minutes keeping the temperature at -5 °C. The solution was allowed to warm to room temperature and stirred overnight. The product was extracted with diethyl ether (*ca*. 3x150 cm^3) and washed with water. The ether layer was concentrated *in vacuo* and treated to flash chromatography (50% ethyl acetate/n-hexane) to yield a orange oil upon concentration *in vacuo* (0.60g, 3.00 mmol) [13% yield].

^1H NMR ($CDCl_3$) 1.35 (3H, m), 4.35 (2H, m), 8.4 (1H, s), 8.9 (1H,

s), 14.4 (1H, s).

Intermediate OX-7

Ethyl α-Oximino-2-methylthiazole-4-acetate.

This was prepared from ethyl-γ-chloro-α-oximino-acetoacetate (1.44g) using the method of Hatanaka *et al.* (*Journal of Medicinal Chemistry*, 1973, 16(9), 978-984) to yield the titled compound (0.64g).

^{1}H NMR ($CDCl_3$) 1.35 (3H, t), 2.7 (3H, s), 4.35 (2H, q), 8.2 (1H, s).

Ethyl γ-Chloro-α-oximinoacetoacetate.

This was prepared from ethyl oximinoacetoacetate (1.73g) using the method of Hatanaka *et al.* (*Journal of Medicinal Chemistry*, 1973, 16(9), 978-984) to yield the titled compound (1.44g).

^{1}H NMR ($CDCl_3$) 1.25 (3H, t), 4.3 (2H, q), 4.55 (2H, s), 9.45 (1H, s), contains 20% starting material by NMR.

Ethyl Oximinoacetoacetate

This was prepared from ethyl acetoacetate (10.00g) using the method of Fischer (*Organic Synthesis Coll. Vol. 3*, 513-516) to yield the titled compound (12.45g).

^{1}H NMR ($CDCl_3$) 1.25 (3H, t), 2.35 (3H, s), 4.3 (2H, q), 8.8 (1H, br.).

Preparation of Intermediates AL-1 - AL-3

The following compounds were prepared according to the indicated method (Method AL-A or Method AL-B) from the indicated starting materials, unless otherwise described.

Intermediate AL-1

R-3-Bromo-(1-t-butoxycarbonylamino-2-hydroxyethyl)benzene.

Method AL-A

Sodium hydroxide (3.33 g, 83.25 mmol) was dissolved in water (220 mL), and 20 mL of the resulting solution was removed and added to potassium osmate (410 mg, 1.11 mmol). The remaining sodium hydroxide solution (200 mL) was added to a stirred solution of *t*-butyl carbamate (9.9 g, 84.5 mmol) in *n*-propanol (110 mL) followed by freshly prepared *t*-butyl hypochlorite (9.65 mL; 83.5 mmol). After stirring for 5 min, the solution was cooled to 0 °C. A solution of $(DHQD)_2$PHAL (1.30 g, 1.67 mmol) in *n*-propanol (110 mL) was added, followed by a solution of 3-bromostyrene (5 g, 27.31 mmol) in n-propanol (220 mL), followed by dropwise addition of the potassium osmate/sodium hydroxide solution. The reaction was stirred overnight. Saturated aqueous sodium sulfite (150 mL) was added, and the reaction was stirred for 15 min. The aqueous layer was separated and extracted with ethyl acetate (3x 200 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of solvent under vacuum gave the crude product which was purified by chromatography (silica, 3:2 hexane:ethyl acetate then rechromatographed loading with toluene, gradient elution with hexane - 4:1 hexane:ethyl acetate) to give the title product (4.18 g, 49%).

Melting Point = 90-91 °C
^{1}H NMR ($CDCl_3$).

Intermediate AL-2

R-3-Methoxycarbonyl-(1-t-butoxycarbonylamino-2-hydroxy-ethyl)benzene.

Method AL-B

In a glass liner containing a stirrer bar was placed $Pd(OAc)_2$ (871 mg, 3.88 mmol), PPh_3 (1.96 g, 7.47 mmol, NaOAc (1.48 g, 18.04 mmol) and DMF (82 mL). To this stirred solution was added a solution of R-3-bromo-(1-t-butoxy-carbonylamino-2-hydroxyethyl)benzene (4.27 g, 13.5 mmol) in MeOH (82 mL). The resulting solution was purged with nitrogen and placed in a stirred pressure vessel. The system was

charged to 4.1 bar (60 psig) of CO and heated at 95 °C for 36 h. The mixture was cooled to room temperature, filtered through diatomaceous earth, and partitioned between ethyl acetate and water. The organic layer was washed with water (3x) and brine (1x) and dried over $MgSO_4$. Removal of solvent under vacuum gave the crude product which was purified by chromatography (silica gel, gradient elution with 30-35% ethyl acetate/hexane) to provide the title product (3.53 g, 89%).

Melting Point = 73-75 °C with decomposition
^1H NMR ($CDCl_3$).
API-MS, m/e = 240 ($M-C_4H_9+1$).

Intermediate AL-3

R-3-Cyano-(1-t-butoxycarbonylamino-2-hydroxyethyl)benzene.

Prepared from 3-cyanostyrene using Method AL-A. 3-Cyanostyrene was prepared using the method described below.

Melting Point = 76 °C.
^1H NMR ($CDCl_3$).

Preparation of 3-Cyanostyrene

To a stirred suspension of methyltriphenylphosphonium bromide (75 g, 209.71 mmol) in dry THF (750 mL) at 0 °C under nitrogen was added dropwise *n*-BuLi (83 mL, 2.5 M in hexanes, 207.50 mmol). The mixture was warmed to room temperature. 3-Cyanobenzaldehyde (25 g, 190.65 mmol) was added as a solid in 5 g batches, and the mixture was stirred at room temperature overnight. The reaction was quenched in water, and the solvent was removed under vacuum. The residue was dissolved in the minimal amount of THF, and triphenylphosphine oxide was precipitated using ether. The solid was filtered through diatomaceous earth, and the filtrate was concentrated. Distillation by Kugelrhor at 90 °C/33 Pa (0.25 mm Hg) gave the product as a colorless oil (15.5 g, 62%).

Boiling Point = 90 °C at 0.25 mmHg.
^1H NMR ($CDCl_3$).

Preparation of Intermediates PAE-1 - PAE-16

The following compounds were prepared according to the indicated method (Method PAE-A, Method PAE-B, Method PAE-C, Method PAE-D or PAE-E) from the indicated starting materials, unless otherwise described.

Intermediate PAE-1

Boc-D,L-(2-pyridinyl)glycine Ethyl Ester.

Method PAE-A

To a solution of ethyl hydroxyimino-pyridin-2-yl-acetate (7.8 g, 40.15 g) in ethanol (175 mL) and glacial acetic acid (20 mL) was added 5% Pd/C, and the mixture was shaken in a hydrogenation apparatus under an atmosphere of hydrogen at 4.1 bar (45 psig) for 4 h. The mixture was filtered through diatomaceous earth and concentrated in vacuo. The residue was dissolved in THF/H_2O (1/1, 240 mL) and treated with di-tert-butyl dicarbonate (14.23 g, 65.2 mmol) and sodium bicarbonate (27.4 g, 326 mmol). After stirring at room temperature for 2 h, the solution was concentrated in vacuo and the residue was partitioned between EtOAc and water. The organic phase was washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was purified via chromatography over silica gel, eluting with a stepwise gradient of 10-20% ethyl acetate in dichloromethane to give 8.11 g (72%) of the title compound as a yellow oil.

1H-NMR
IS-MS, m/e 281.1 (M+1)

Intermediate PAE-2

Boc-D,L-(3-pyridinyl)glycine Ethyl Ester.

Prepared from ethyl hydroxyimino-pyridin-3-yl-acetate using Method PAE-A.

1H-NMR
IS-MS, m/e 281.1 (M+1)

Intermediate PAE-3

Boc-D,L-(8-quinolinyl)glycine Ethyl Ester.

Method PAE-B

To a stirring solution of ethyl hydroxyimino-quinolin-8-yl-acetate (2.4 g, 9.8 mmol) in 50% aq. formic acid (50 mL) at 0 °C was added zinc dust (2 g, 31 mmol). After 1 min, the mixture was filtered through diatomaceous earth and the filtrate was loaded onto an SCX column. After washing the column with methanol, the product was eluted with a 3 to 1 mixture of dichloromethane and (2 N NH_3 in methanol). The product containing fractions were combined and concentrated in vacuo to give 2.24 g of light orange oil (IS-MS, m/e 231.0 (M+1)).

The oil (2.14 g, 9.3 mmol) was dissolved in THF (40 mL) and to this stirring solution was added triethylamine (1.4 mL, 10.2 mmol), followed by di-tert-butyl-dicarbonate (2.1 g, 9.8 mmol). After 45 min, the solvent was removed in vacuo and the residue was partitioned between ethyl acetate and water. The organic phase was then washed with satd aq. $NaHCO_3$, dried with Na_2SO_4, filtered and concentrated in vacuo. The residue was dissolved in a minimum volume of dichloromethane and chromatographed over silica gel, eluting with 5% ethyl acetate in hexanes. The product containing fractions were combined and concentrated to give 2.5 g (81%) of the title compound.

1H-NMR
IS-MS, m/e 331.0 (M+1)

Intermediate PAE-4

Boc-D,L-(5-quinolinyl)glycine Ethyl Ester

Prepared from ethyl hydroxyimino-quinolin-5-yl-acetate using Method PAE-B.

1H-NMR
IS-MS, m/e 331.0 (M+1)

Intermediate PAE-5

N-4-Methoxybenzoyl-N-2,4-dimethoxybenzyl-D,L-(2-trifluoromethylphenyl)glycine Methyl Ester.

Method PAE-C

To 2-trifluoromethylbenzaldehyde (1 g, 5.7 mmol) with stirring was added 2,4-dimethoxybenzylamine (0.86 mL, 5.7 mmol) and methanol (2 mL). After 5 min, the solution was diluted with toluene 100 mL and concentrated in vacuo (twice). The residue was then dissolved in anhydrous methanol (12 mL) and 1,1-dimethyl-2-(methoxycarbonyloxy)ethyl isonitrile [Tetrahedron, 55 (1999) 7411-7420] (0.9 g, 5.7 mmol) was added, followed by 4-methoxybenzoic acid (0.87 g, 5.7 mmol). After stirring for 72 h, the solvent was removed in vacuo and the residue was chromatographed over silica gel, eluting with a step gradient of 30% ethyl acetate in hexanes through 50% ethyl acetate in hexanes. The product containing fractions were combined and concentrated in vacuo; and then the residue was dissolved in ethyl acetate, washed with satd aq. $NaHCO_3$, dried with Na_2SO_4, filtered and concentrated to give 1.76 g (48%) of thick oil (NMR, IS-MS, m/e 633.0 (M+1)).

The oil (0.5 g, 0.79 mmol) was then dissolved in toluene (5 mL) and concentrated in vacuo (twice) to give a white foam. The residue was then dissolved in THF (3 mL) and potassium tert-butoxide (0.11 g, 0.95 mmol) was added. After 15 min, 12 N HCl (0.079 mL, 0.95 mmol) was added and the solution was allowed to stand overnight in the refrigerator. The next morning, the solvent was removed and the residue was chromatographed over silica gel, eluting with 30% ethyl acetate in hexanes. The product containing fractions were combined and concentrated to give 0.32 g (79%) of the title compound.

1H-NMR
IS-MS, m/e 518.0 (M+1)

Intermediate PAE-6

BOC-D,L-(5-thiazolyl)glycine ethyl ester.

To a r.b. flask (250cm^3), D,L-(5-thiazolyl)glycine ethyl

ester (4.60g, 24.7 mmol) was added to tetrahydrofuran (*c.a.* 100cm^3) with stirring to give a yellow solution. BOC anhydride (5.439g, 24.948 mmol) and triethyl amine (3.79 cm^3, 2.75g, 27.17 mmol) were then added with stirring for 1 hour. Reaction monitored by TLC (60% hexane/ethyl acetate; s.m. r.f 0.05, prod. r.f. 0.5.). The reaction concentrated *in vacuo* and product taken up in ethyl acetate (*c.a.* 150 cm^3), washed with 5% hydrochloric acid solution (*c.a.* 30 cm^3), and saturated bicarbonate (*ca.* 30cm^3). Ethyl acetate layer was dried over magnesium sulphate and evaporated to dryness to give an orange oil (7.42g, ~24.70 mmol) [~100% Yield].

^{1}H NMR ($CDCl_3$); 1.30 (3H, t), 1.48 (9H, s), 4.28 (2H, q), 5.68 (1H, br.), 7.88 (1H, s), 8.78 (1H, s).

D,L-(5-Thiazolyl)glycine Ethyl Ester.

To a r.b. flask (250 cm^3), was added 5-thiazolyl-oximinoacetic acid ethyl ester (6.37g, 31.825 mmol) to ethanol (*c.a.* 80cm^3) with stirring. 50% Formic acid solution (50 cm^3) was added with zinc dust (5.10g, 81.83 mmol) and allowed to stir overnight. Reaction monitored by TLC (60% hexane/ethyl acetate; s.m. r.f 0.3, prod. r.f. 0.05.).
Reaction solution filtered over celite and filtrate concentrated *in vacuo*. This was basified to pH 9 with anhydrous potassium carbonate and product taken up in 3:1 chloroform/isopropanol solution (*c.a.* 200 cm^3). This was washed with saturated bicarbonate (*c.a.* 50 cm^3), dried over magnesium sulphate and concentrated *in vacuo* to give a brown oil (4.60g, 24.70 mmol) [78% Yield].

^{1}H NMR ($CDCl_3$); 1.25 (3H, t), 1.95 (2H, br.), 4.22 (2H, q), 4.85 (1H, s), 7.80 (1H, s), 8.70 (1H, s).

Intermediate PAE-7

N-Boc-D,L-(4-thiazolyl)glycine ethyl ester

To a solution of D,L-(4-thiazolyl)glycine ethyl ester

(0.460g, 2.470 mmol) in tetrahydrofuran (20 cm^3), was added di-*tert*-butyl dicarbonate (0.530g, 2.470 mmol) and triethylamine (0.344 cm^3, 2.470 mmol). This was allowed to stir for 1 hour and the solution concentrated *in vacuo*. The oil was taken up in ethyl acetate (*c.a.* 50 cm^3) washed with 0.5% hydrochloric acid solution (*c.a.* 20 cm^3), and saturated sodium bicarbonate solution (*c.a.* 20 cm^3). This was then dried over magnesium sulphate and concentrated *in vacuo* to yield an orange oil (0.709g, 2.477 mmol) [~100% yield].

^1H NMR ($CDCl_3$) 1.15 (3H, t), 1.35 (9H, s), 4.1 (2H, m), 5.45 (1H, d), 5.75 (1H, d), 7.3 (1H, d), 8.7 (1H, d).

D,L-(4-Thiazolyl)glycine Ethyl Ester.

This was prepared from ethyl-α-oximino-thiazole-4-acetate (0.60g) using the method of Hatanaka *et al.* (*Journal of Medicinal Chemistry,* 1973, 16(9), 978-984) to yield the titled compound (0.46g).

^1H NMR ($CDCl_3$) 1.25 (3H, t), 1.8-2.3 (2H, br.), 4.1 (2H, m), 4.75 (1H, s), 7.25 (1H, d), 8.7 (1H, d).

Intermediate PAE-8

N-Boc-D,L-(2-methylthiazol-4-yl)glycine Ethyl Ester

To a solution of D,L-(2-methylthiazol-4-yl)glycine ethyl ester (0.397g, 1.982 mmol) in tetrahydrofuran (20 cm^3), was added di-*tert*-butyldicarbonate (0.475g, 2.180 mmol) and triethylamine (0.304 cm^3, 2.180 mmol). This was allowed to stir for 1 hour and the solution concentrated *in vacuo*. The oil was taken up in ethyl acetate (*c.a.* 50 cm^3) washed with 0.5% hydrochloric acid solution (*c.a.* 20 cm^3), and saturated sodium bicarbonate solution (*c.a.* 20 cm^3). This was then dried over magnesium sulphate and concentrated *in vacuo* to yield a yellow oil (0.654g, 2.177 mmol) [~100% yield].

^1H NMR ($CDCl_3$) 1.1 (3H, s), 1.35 (9H, s), 2.6 (3H, s), 4.15 (3H, m), 5.3 (1H, d), 5.7 (1H, s), 7.0 (1H, s).

D,L-(2-Methylthiazol-4-yl)glycine Ethyl Ester.

This was prepared from ethyl-α-oximino-2-methylthiazole-4-acetate (0.62g) using the method of Hatanaka *et al.* (*Journal of Medicinal Chemistry,* 1973, 16(9), 978-984) to yield the titled compound (0.40g).

^1H NMR ($CDCl_3$) 1.15 (3H, t), 1.95 (2H, br.), 2.6 (3H, s), 4.15 (2H, m), 4.65 (1H, s), 6.95 (1H, s).

Intermediate PAE-9

Boc-R-(4-Hydroxyphenyl)glycine methyl ester

To a stirred mixture of R-(4-hydroxyphenyl)glycine methyl ester hydrochloride (14g) and sodium bicarbonate (11.7g) in THF (150ml) and water (50ml), was added in one portion, di- t-butyl dicarbonate (15.9g). The mixture was stirred rapidly to allow thorough mixing for 4h. Hexane (75ml) was added and the organic layer separated and washed with sat. sodium bicarbonate solution, then brine and then dried with magnesium sulphate. The drying agents was filtered off and washed with a little THF and evaporated to dryness, finishing with a high vacuum pump to remove the last traces of di- t-butyl dicarbonate. Yield 19.7g, 96%.

^1H NMR

R-(4-Hydroxyphenyl)glycine Methyl Ester Hydrochloride.

To a dry 250ml three necked round bottom flask, equipped with a low temperature thermometer, a septum for nitrogen coverage and another for introduction of thionyl chloride by syringe, was added R-4-hydroxyphenylglycine (12.5g) and dry methanol (24ml). The mixture was stirred (magnetic stirrer) and cooled to an internal temperature of -20°C using cardice/acetone. Using a syringe, thionyl chloride was added <u>dropwise</u> to the cooled mixture over a period of 10min. (Care:

the reaction of thionyl chloride with methanol is very exothermic and rate of addition should be such that the thionyl chloride is efficiently stirred into the mixture and that the temperature does not rise above -20°C. Once the addition was complete the mixture was allowed to warm to room temperature overnight (16-18hr). Dry ether (150ml) was added and the white ppt. that formed was filtered off, washed with a little more ether and dried. Yield 15.5g 95%.

^{1}H NMR

Intermediate PAE-10

Boc-R-(4-Trifluoromethanesulphonyloxyphenyl)glycine Methyl Ester Hydrochloride

To a stirred solution of Boc-R-(4-hydroxyphenyl)glycine methyl ester 19g in dichloromethane 400ml was added 2,6-lutidine 9.44ml and 4-dimethylaminopyridine 1.65g and the mixture cooled in an ice bath. Trifluoromethananesulphonic anhydride 13.74ml was added over a period of 5min and then the reaction left to warm to room temperature over 4h. The organic solution was washed with water, 2 x 150ml, 1N HCl 2 x 150ml and the saturated sodium bicarbonate 150ml. The organics were dried with magnesium sulphate and then evaporated to and oil. The mixture was purified using flash chromatography (SiO_2 250g eluting with 1:1 hexane/dichloromethane and then neat dichloromethane). Pure product fractions were combined and evaporated, finishing with a high vacuum pump to remove all traces of solvent, to give a white solid, 19g 77%.

^{1}H NMR

Intermeidate PAE-11

Boc-R-(4-Methoxycarbonylphenyl)glycine Methyl Ester.

Method PAE-D

Boc-R-4-trifluoromethanesulphonyloxyphenylglycine methyl ester (15g), methanol (32.6ml), bis-1,3-diphenyl-

phosphinylpropane (448mg), palladium (II) acetate (255mg), triethylamine (10.2ml) and dimethylformamide (72ml) were placed in the glass liner of the Parr reactor and the reactor assembled. The vessel was pressurised to ~10psi with nitrogen and the gas released (repeated five times to remove all oxygen from the system). Carbon monoxide gas was then carefully introduced (use extreme care -the gas cylinder is pressurised to far beyond the bursting disc pressure of the Parr, ideally use a pressure regulator to reduce the pressure to ~100psi) to ~20psi and released three times (into the back of a fume hood). Carbon monoxide was then added to ~100psi and the stirrer started. The vessel was <u>slowly</u> heated to 65°C internal temperature and then stirred at 65°C overnight. (At the early stages more carbon monoxide was added to maintain ~100psi) A sample was removed after 18h and examined by tlc. When complete, the reaction was cooled to ~30°C, the gas released and the vessel flushed five times with nitrogen as before. The reaction mixture was partitioned between ethyl acetate and water and the organic layer washed with 1M hydrochloric acid and then saturated sodium bicarbonate. The solution was dried with $MgSO_4$ and evaporated. Flash chromatography of the resulting oil gave the product, pure by tlc, 10.6g 90%.

^1H NMR

Intermediate PAE-12

Boc-R-(4-Benzyloxycarbonylphenyl)glycine Methyl Ester.

Prepared from Boc-R-4-trifluoromethanesulphonyloxy phenylglycine methyl ester and benzyl alcohol using Method PAE-D.

^1H NMR

Intermediate PAE-13

Boc-R-(4-Carboxyphenyl)glycine Methyl Ester.

Boc-R-(4-benzyloxycarbonylphenyl)glycine methyl ester (500mg) was dissolved in THF containing Pd/C 10% (100mg) and hydrogenated at 1atm for 2h. Removal of the catalyst by

filtration and evaporation of solvent gave Boc-R-(4-carboxyphenyl)glycine methyl ester (330mg, 87%).

^1H NMR

Intermediate PAE-14

Boc-R-(4-carboxamidophenyl)glycine Methyl Ester.

Method PAE-E

To a solution of Boc-R-(4-carboxyphenyl)glycine methyl ester (3.5g) in DMF 30ml was added EDCI (2.60g 1.36 mmol) and HOBt (1.4g 10.4mmol) and the mixture stirred for 10min before cooling in a ice bath and bubbling in ammonia gas for 5min. The mixture was stirred for 2h at room temperature and then diluted with ethyl acetate and washed with water. The aqueous solution was extracted with a little ethyl acetate and the combined organics washed with brine. The organic solution was evaporated to an oil which was purified by flash chromatography (SiO_2 - dichloromethane/ ethyl acetate 0 - 25%) to give Boc-R-(4-carboxamidophenyl)glycine methyl ester (1.7g 48%).

^1H NMR

Intermediate PAE-15

Boc-R-(4-methylcarboxamidophenyl)glycine Methyl Ester.

Prepared from Boc-R-(4-carboxyphenyl)glycine methyl ester and methylamine using Method PAE-E.

^1H NMR

Intermediate PAE-16 (pb0-h5u-119, px099940)

N-4-Methoxybenzoyl-N-2,4-dimethoxybenzyl-D,L-(quinolin-4-yl)glycine Methyl Ester.

Prepared from quinoline-4-carboxaldehyde using Method PAE-C.

^1H NMR

Preparation of Intermediates PAA-1 - PAA-20

The following compounds were prepared according to the indicated method (Method PAA-A, Method PAA-B, Method PAA-C, Method PAA-D, or Method PAA-E) from the indicated starting materials, unless otherwise described.

Intermediate PAA-1

Boc-D,L-(2-chlorophenyl)glycine.

Method PAA-A

2-Chlorobenzaldehyde (20 mmol, 2.252 mL) and 2,4-dimethoxybenzylamine (20 mmol, 3.004 mL) were added together and stirred for 2 hours. DCM (5ml) was added and any water separated and removed. tert-Butyl isonitrile (20 mmol, 2.262 mL) was added and stirred for 10mins followed by acetic acid (20 mmol, 1.145 mL). Stirring was continued for 3 days. The reaction mixture was then treated with TFA (30ml) and triethylsilane (5ml). After 3 hours the mixture was evaporated to dryness, 6M HCl (100ml) added and the whole refluxed overnight at 130°C, stirring rapidly. The mixture was allowed to cool and extracted with EtOAc (50ml x2) the aqueous fraction was evaporated to dryness and treated with 2M NaOH solution. The mixture was extracted with EtOAc (50ml x2) excess boc anhydride (5.2g) in dioxane (20ml) was added to the aqueous fraction and stirred overnight. The mixture was extracted with diethyl ether (100ml x2) acidified to pH 1 (cHCl) and extracted with EtOAc (50ml x2). The combined organic fractions were washed with water and evaporated to dryness under high vacuo The product Boc -2-chlorophenyl-glycine (4.252g, 74.5%)

^1H nmr (CD_3CN/D_2O) 7.3 (4H, m); 5.5 (1H, s); 1.3 (9H, s). MS 286 (M+1)

Intermediate PAA-1'

(R)-Benzyloxycarbonyl-(2-chlorophenyl)glycine.

Prepared from 2-chlorostyrene using the method of Sharpless *et al* J.A.C.S. (1998) Vol120 No.6 1207-1217.

Intermediate PAA-2

Boc-D,L-(3-fluorophenyl)glycine.

Prepared from 3-fluorobenzaldehyde using Method PAA-A.

^1H nmr (CD_3CN/D_2O) 7.3 (1H, m), 7.1(3H, m); 5.2 (1H, s); 1.3 (9H, s). MS 270 (M+1)

Intermediate PAA-3

Boc-D,L-(4-fluorophenyl)glycine.

Prepared from 4-fluorobenzaldehyde using Method PAA-A.

^1H nmr (CD_3CN/D_2O) 7.3 (2H, m); 6.9 (2H, m), 5.0 (1H, s); 1.3 (9H, s). MS 270 (M+1)

Intermediate PAA-4

Boc-D,L-(2-methylphenyl)glycine.

Prepared from 2-methylbenzaldehyde using Method PAA-A.

^1H nmr (CD_3CN/D_2O) 7.3 (4H, m); 5.5 (1H, s); 2.5 (3H, s); 1.3 (9H, s). MS 266 (M+1)

Intermediate PAA-5

Boc-D,L-(3-thienyl)glycine.

Prepared from 3-thiophenecarboxaldehyde using Method PAA-A.

^1H nmr (CD_3CN/D_2O) 7.5 (2H, m); 7.1 (1H, d); 5.3 (1H, s); 1.3 (9H, s). MS 258 (M+1)

Intermediate PAA-6

Boc-D,L-(2-fluorophenyl)glycine.

Was obtained by treating D,L-2-fluorophenylglycine (Aldrich) with Boc anhydride (1.1eq) and 2M NaOH (1eq) in

Ethanol. Aqueous work up as described above yielded the protected amino acid.

^1H NMR

Intermediate PAA-7

Boc-D,L-(2-methoxyphenyl)glycine.

Prepared from 2-methoxybenzaldehyde using Method PAA-A.

^1H NMR

Intermediate PAA-8

Boc-D,L-(2-trifluoromethyl)phenylglycine.

Prepared from 2-trifluoromethylbenzaldehyde using Method PAA-A.

^1H NMR

Intermediate PAA-9

Boc-D,L-(8-quinolinyl)glycine.

Method PAA-B

To a stirring solution of Boc-D,L-(8-quinolinyl)glycine ethyl ester (2.29 g, 6.93 mmol) in 1,4-dioxane (11 mL) was added a solution of LiOH hydrate (0.32 g, 7.6 mmol) in water. After 2 h, the solvents were removed in vacuo and the residue was dissolved in water and washed with diethyl ether. The aqueous phase was then acidified to pH 3 with solid citric acid and extracted with ethyl acetate. The organic phase was then washed with brine, dried with Na_2SO_4, filtered and concentrated to give 2.06 g (98%) of the title compound.

1H-NMR
IS-MS, m/e 303.0 (M+1)

Intermediate PAA-10

Boc-D,L-(5-quinolinyl)glycine.

Prepared from Boc-D,L-(5-quinolinyl)glycine ethyl ester using Method PAA-B.

1H-NMR
IS-MS, m/e 303.0 (M+1)

Intermediate PAA-11

Boc-D-(3-bromophenyl)glycine.

Prepared from R-3-bromo-(1-t-butoxycarbonylamino-2-hydroxyethyl)benzene using Method PAA-C.

Melting Point = 130-132 °C with decomposition
^{1}H NMR ($CDCl_3$)
API-MS, m/e = 286 ($M-CO_2H+1$)

Intermediate PAA-12

Boc-D-(3-methoxycarbonylphenyl)glycine.

Method PAA-C

To a stirred solution of R-3-methoxycarbonyl-(1-t-butoxycarbonylamino-2-hydroxyethyl)benzene (338 mg, 1.14 mmol) in acetone (7.2 mL) was added 5% $NaHCO_3$ (3 mL). The reaction mixture was cooled to 0 °C. To the stirred suspension was added KBr (14 mg, 0.12 mmol), TEMPO (181 mg, 1.16 mmol) and NaOCl dropwise (2.81 mL, 5.25%). After 1 h at 0 °C, TEMPO (136 mg, 0.88 mmol) and NaOCl (1.09 mL; 5.25%) were added. The reaction was stirred for a further 0.5 h at 0 °C and 5% $NaHCO_3$ (4.3 mL) was added. The reaction was allowed to warm to room temperature overnight. Acetone was removed under vacuum and the crude product was partitioned between ethyl acetate and water. The aqueous layer was washed with ethyl acetate (2x) and acidified to pH 5 with 10% citric acid and extracted with ethyl acetate (4x). The combined organic extracts were dried over $MgSO_4$. Removal of solvent under vacuum gave the product (305 mg, 86%).

^{1}H NMR ($CDCl_3$)
API-MS, m/e = 254 ($M-C_4H_9+1$)

Intermediate PAA-13

Boc-D-(3-cyanophenyl)glycine.

Prepared from R-3-cyano-(1-t-butoxycarbonylamino-2-hydroxyethyl)benzene using Method PAA-C.

^1H NMR ($CDCl_3$)
API-MS, m/e = 221 ($M-C_4H_9+1$)

Intermediate PAA-14

Boc-D-(3-ethanesulfonylaminophenyl)glycine.

To a stirring solution of 3—(ethanesulfonylamino-phenyl)glycine (20 g, 77.43 mmol) and sodium carbonate (8.2 g, 77.43 mmol) in 3:1 THF:water (200 mL) at 0 °C, was added di-tert-butyl dicarbonate (18.5 g, 85.17 mmol). After stirring for 30 min, the cold bath was removed; and after an additional 30 min at room temperature the solvent was removed; and the residue was partitioned between ethyl acetate and water. The aqueous layer was acidified to pH 2 with $KHSO_4$ and extracted twice with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried with Na_2SO_4, filtered and concentrated in vacuo to give 17.51 g (63%) of a white solid.

1H-NMR
IS-MS, m/e 357.0 (M-1)

Intermediate PAA-15

N-Boc-D,L-(5-thiazolyl)glycine.

To a r.b. flask (150 cm^3), was added Boc-D,L-(5-thiazolyl)glycine ethyl ester (7.00g, 24.70 mmol) to ethanol (*c.a.* 100cm^3) with stirring. 2M Sodium hydroxide solution (25 cm^3, 50 mmol) was added and allowed to stir for 1 hour. Reaction monitored by TLC (60% hexane/ethyl acetate; s.m. r.f 0.5, prod. r.f. 0.).

Reaction concentrated *in vacuo* and product taken up in saturated bicarbonate (*c.a.* 50 cm^3) and washed with ethyl

acetate (*c.a.* 30 cm^3). Aqueous layer was acidified to pH 2 with concentrated hydrochloric acid and product extracted with 3:1 chloroform/isopropanol solution (*c.a.* 3x60cm^3). The organic layer was dried over magnesium sulphate and evaporated to dryness to give an orange solid (4.47g, 17.30 mmol) [74% Yield].

^1H NMR ($CDCl_3$); 1.35 (9H, s), 5.60 (1H, d), 5.83 (1H, d), 7.88 (1H, s), 8.80 (1H, s).

Intermediate PAA-16

N-Boc-D,L-(4-thiazolyl)glycine.

Method PAA-D

To a solution of N-Boc-D,L-(4-thiazolyl)glycine ethyl ester (0.700g, 2.470 mmol) in methanol (*c.a.* 15 cm^3), was added 2M sodium hydroxide (2.47 cm^3, 4.940 mmol) and allowed to stir for 90 minutes. The solution was concentrated *in vacuo* and taken up in water (*c.a.* 20 cm^3). The aqueous solution was washed with ethyl acetate (*c.a.* 20 cm^3), and then acidified to pH 2 with 5% hydrochloric acid solution (*c.a.* 50 cm^3). The product was extracted with ethyl acetate (*c.a.* 3x30 cm^3), dried over magnesium sulphate, and concentrated *in vacuo* to yield a pale yellow oil (0.582g, 2.254 mmol) [91% yield].

^1H NMR ($CDCl_3$) 1.35 (9H, s), 5.5 (1H, d), 5.8 (1H, d), 7.35 (1H, d), 8.75 (1H, d), 9.8-10.2 (1H, br.).

Intermediate PAA-17

N-Boc-D,L-(2-methylthiazol-4-yl)glycine.

Prepared from N-Boc-D,L-(2-methylthiazol-4-yl)glycine ethyl ester using Method PAA-D.

^1H NMR ($CDCl_3$) 1.35 (9H, s), 2.6 (3H, s), 5.4 (1H, d), 5.9 (1H, s), 7.1 (1H, s).

Intermediate PAA-18

N-Boc-D,L-(2-Benzyloxycarbonylamino-4-thiazolyl)glycine.

Is prepared from D,L-(2-benzyloxycarbonylamino-4-thiazolyl)glycine. The benzyloxycarbonyl protecting group is removed from the thiazolyl amino group at a convenient point in the preparation of a final compound using a conventional method, such as, for example, heating a solution of an intermediate in HBr/acetic acid at 60 °C, followed by evaporation and a conventional isolation, such as by using SCX ion exchange chromatography.

D,L-(2-Benzyloxycarbonylamino-4-thiazolyl)glycine was prepared by the method of Hardy, K.; Harrington, F. and Stachulski, A. - J. Chem. Soc. Perkin Trans I (1984) 1227-1235.

Intermediate PAA-19

Boc-R-(4-methoxycarbonylphenyl)glycine.

To a solution of Boc-R-(4-methoxycarbonylphenyl)glycine methyl ester 692mg in THF 10ml was added a solution of lithium hydroxide hydrate 90mg in water 7ml. The mixture immediately became cloudy and over 15min cleared. After 30min, tlc showed the reaction to be complete. Ethyl acetate 20ml and water 20ml were added and the aqueous layer separated. The aqueous solution was acidified with 2M hydrochloric acid and extracted with ethyl acetate (3 x 20ml). The organic solution was then washed with water x 2 and brine x 2, dried with $MgSO_4$ and evaporated to give the mono-ester (650mg, 98%), pure by tlc.

^{1}H NMR

Intermediate PAA-20

Boc-R-(4-Methoxyphenyl)glycine.

Boc-R-(4-hydroxyphenyl)glycine methyl ester was converted to Boc-R-4-methoxyphenylglycine using the alkylation method described by Basak *et al.*(Tetrahedron Lett. 1998, 39 (27),

4883-4886) followed by hydrolysis of the methyl ester with lithium hydroxide in aqueous THF.

^1H NMR

Intermediate PAA-21

N-4-Methoxybenzoyl-N-2,4-dimethoxybenzyl-D,L-(2-trifluoromethylphenyl)glycine.

Prepared from N-4-methoxybenzoyl-N-2,4-dimethoxybenzyl-D,L-(2-trifluoromethylphenyl)glycine methyl ester using Method PAA-B (3 equivalents of LiOH hydrate).

^1H NMR

IS-MS, m/e 503.9 (m + 1)

Intermediate PAA-22

N-4-Methoxybenzoyl-N-2,4-dimethoxybenzyl-D,L-(thien-2-yl)-glycine.

Method PAA-E

To a solution of 2-thiopheneboronic acid (5.0 g, 39.0 mmol, 1 equiv) in 275 mL of methylene chloride at rt was added 3,4-dimethoxybenzylamine (5.89 mL, 39.0 mmol, 1 equiv) followed by glyoxylic acid monohydrate 3.6 g, 39 mmol, 1 equiv). The reaction was allowed to stir for 56 hours at rt after which time the resultant precipitate was filtered and washed with methylene chloride to afford 9.3 g (78%) of N-2,4-dimethoxybenzyl-D,L-(thien-2-yl)glycine as an off-white solid (IS-MS, m/e 308 (m + 1)).

A portion of the solid (5.0 g, 16.3 mmol, 1 equiv.) was dissolved in acetone (20 mL) and 1N sodium hydroxide (20 mL) at rt. To this solution was simultaneously added anisoyl chloride (2.78 g, 16.3 mmol, 1 equiv.) in 20mL of acetone and 2N sodium hydroxide in dropwise fashion. After stirring at rt for 1 hour, the reaction was cooled to 0C and was acidified to pH2-3. Diethyl ether was added and the product was extracted into the organic phase. The combined organic phases were washed with brine, dried over sodium sulfate, filtered, and concentrated to

afford 5.1 g (71%) of the titled compound as a white solid.

IS-MS, m/e 440 (m + 1).

Intermediate PAA-23

N-Boc-N-2,4-dimethoxybenzyl-D,L-(thien-2-yl)glycine.

To a solution of N-2,4-dimethoxybenzyl-D,L-(thien-2-yl)glycine (1.0 g, 3.2 mmol, 1 equiv) in 6 mL of acetone and 6 mL of water at rt was added triethylamine (0.97 mL, 7.0 mmol, 2.1 equiv.) followed by addition of BOC-ON (0.76 g, 3.1 mmol, 0.95 equiv). After stirring at rt overnight, the reaction was diluted with water and washed with ether. The aqueous phase was then acidified with 0.5M citric acid and the product was extracted into diethyl ether. The combined organic phases were washed with brine, dried over sodium sulfate, filtered, and concentrated to afford 0.38 g (29%) of the titled compound as a crude yellow oil.

IS-MS, m/e 408 (m +1).

Preparation of Intermediates A-1 - A-8

The following compounds were prepared according to the indicated method (Method A-A or Method A-B) from the indicated starting materials, unless otherwise described.

Intermediate A-1

1-[2-(4-Pyridinyl)ethyl]piperazine hydrochloride.

Method A-A

A. 1-Boc-piperazine (30 g, 285 mmol), 4-vinylpyridine (40 g, 216 mmol) and acetic acid (12.9 g, 215 mmol) were mixed in ethanol (400 mL) and heated to reflux for 18 h. The mixture was cooled to room temperature and concentrated under vacuum. The residue was dissolved in water and ethyl acetate and neutralized with satd $NaHCO_3$. The layers were separated. The water layer was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by

SiO_2 chromatography to provide 1-Boc-4-[2-(4-pyridinyl)ethyl]piperazine (55.9 g, 87%) as an off white solid.

1H-NMR($CDCl_3$)
CI-MS, m/e = 292 (M+1)

B. 1-Boc-4-[2-(4-pyridinyl)ethyl]piperazine (25 g, 85.8 mmol) was dissolved in methanol (100 mL) and was cooled to 0 °C. Saturated HCl in methanol (100 mL) was added, and the mixture allowed to warm to room temperature for 1 h. The mixture was concentrated under vacuum and provided 1-[2-(4-pyridinyl)ethyl]piperazine hydrochloride (23.8 g, 92%) as a white solid.

1H-NMR(CD_3OD)
CI-MS, m/e = 192 (M+1)

Alternatively, 1-Boc-4-[2-(4-pyridinyl)ethyl]piperazine (1.0 g, 3.43 mmol) was dissolved in ethyl ether. Ethyl acetate (15 mL) saturated with HCl was added, and the mixture stirred for 30 min at room temperature. The mixture was concentrated under vacuum and provided 1-[2-(4-pyridinyl)-ethyl]piperazine hydrochloride (900 mg, 87%) as a tan solid.
1H-NMR(CD_3OD)
CI-MS, m/e = 192 (M+1)

Intermediate A-2

1-[2-(2-Pyridinyl)ethyl]piperazine.

Prepared from Boc-piperazine and 2-vinylpyridine using Method A-A.

1H-NMR(CD_3OD)
CI-MS, m/e = 192 (M+1)

Intermediate A-3

1-[2-(2-Pyrazinyl)ethyl]piperazine.

Prepared from Boc-piperazine and 2-vinylpyrazine using Method A-A.

1H-NMR (CD_3OD)
CI-MS, m/e = 193 (M+1)

Intermediate A-4

1-[2-(3-Pyridazinyl)ethyl]piperazine.

Prepared from Boc-piperazine and 3-vinylpyridazine (prepared using the method described in *J. Chem. Soc., Chem. Commun.* 1985, 1632-1633) using Method A-A.

1H NMR (CD_3OD)
API-MS, m/e = 193 (M+1)

Intermediate A-5

1-[2-(3-Pyridinyl)ethyl]piperazine.

Method A-B

1-Boc-4-[(3-pyridinyl)acetyl]piperazine (8.0 g, 26.2 mmol) was added to a solution of borane·THF (2.0 M in THF, 39.5 mL, 78.6 mmol) in THF (200 mL) at 0 °C. The mixture was heated to reflux for 8 h and cooled to room temperature. The excess borane was quenched with methanol and 3 N HCl. The mixture stirred for 3 h at room temperature, and the solvents were removed under vacuum. The crude product was purified by chromatography (SiO_2, 4:1 CH_2Cl_2:CMA) to provide 1-[2-(3-pyridinyl)ethyl]piperazine (2.82 g, 36%) as a light yellow oil.

1H NMR (CD_3OD)
API-MS, m/e = 192 (M+1)

Intermediate A-6

1-[2-(4-Imidazolyl)ethyl]piperazine.

Prepared from 1-Boc-4-[(4-imidazolyl)acetyl]piperazine using Method A-B.

1H-NMR
IS-MS, m/e 181.2 (M+1)

Intermediate A-7

1-[2-(1-Imidazolyl)ethyl]piperazine.

Prepared from 1-Boc-4-[(1-imidazolyl)acetyl]piperazine using Method A-B.

1H-NMR
IS-MS, m/e 181.4 (M+1)

Intermediate A-8

1-[2-(1-Pyrazolyl)ethyl]piperazine.

Prepared from 1-Boc-4-[(1-pyrazolyl)acetylpiperazine using Method A-B.

1H-NMR
IS-MS, m/e 181.4 (M+1)

Preparation of Intermediates B-1 - B-4

The following compounds were prepared according to the indicated method (Method B-A, Method B-B or Method B-C) from the indicated starting materials, unless otherwise described.

Intermediate B-1

1-Boc-4-[(3-pyridinyl)acetyl]piperazine.

Method B-A

1-Boc-piperazine (12 g, 64 mmol), 3-pyridylacetic acid (8.85 g, 64 mmol), and HOBt (8.64 g, 64 mmol) were dissolved in DMF. To this solution, EDCI (14.7 g, 76.8 mmol) was added in portions. The mixture became homogenous and was stirred for 3 h. The mixture was diluted with water and ethyl acetate. The layers were separated, and the aqueous layer extracted with ethyl acetate. The organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated to provide a yellow solid. The crude product was purified by recrystallization from hexanes:dichloromethane to provide 1-Boc-4-[(3-pyridinyl)acetyl]piperazine (13.5 g, 69%) as a white solid.

1H-NMR($CDCl_3$)
CI-MS, m/e = 306 (M+1)

Intermediate B-2

1-Boc-4-[(imidazol-4-yl)acetyl]piperazine.

Method B-B

To a stirring suspension of sodium 4-imidazolylacetate (0.5 g, 3.4 mmol) in DMF (25 mL) was added diethyl cyanophosphonate (0.6 mL, 4 mmol). After 5 min, Boc-piperazine (0.57 g, 3.1 mmol) was added, followed by a solution of triethylamine (0.47 mL, 3.4 mmol) in DMF (20 mL). After 72 h, the solvent was removed in vacuo and the residue was dissolved in ethyl acetate and washed with satd aq. $NaHCO_3$ and brine, dried with $MgSO_4$, filtered and concentrated to give 0.95 g of pink oil.

1H-NMR
IS-MS, m/e 295.1 (M+1)

Intermediate B-3

1-Boc-4-[(1-imidazolyl)acetyl]piperazine.

Preparation of Starting Materials:

1-Boc-4-bromoacetylpiperazine

To a stirring solution of bromoacetyl bromide (29.8 g, 148 mmol) in THF (250 mL) at 0 °C was added via an addition funnel a solution of Boc-piperazine (25 g, 134 mmol) and triethylamine (14.9 g, 148 mmol) in THF (75 mL). After 1 h, a few grams of ice were added and the mixture was diluted with ethyl acetate and cold water. The layers were separated and the organic phase was washed with 1 M aq. citric acid, brine, satd aq. $NaHCO_3$ and again with brine. The organic phase was then dried with $MgSO_4$, filtered, and concentrated in vacuo to give 38.2 g (93%) of an off-white powder.

1H-NMR

IS-MS, m/e 251.3 ($M-C_4H_9+1$)

Method B-C

To a stirring suspension of NaH (60% dispersion in mineral oil, 2.34 g, 59 mmol) in THF (75 mL) was added imidazole (1.46 g, 22 mmol) in small portions. After complete addition and complete gas evolution, a solution of 1-Boc-4-(bromoacetyl)piperazine (6 g, 19.5 mmol) in THF (40 mL) was added via an addition funnel. After 2 h, the reaction was quenched with the slow addition of water and then diluted with ethyl acetate. The organic phase was washed with satd aq. $NaHCO_3$, followed by brine, then dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was suspended in diethyl ether with sonication, then filtered and dried to give 4.64 g (81%) of an off white powder.

1H-NMR

IS-MS, m/e 295.2 (M+1)

Intermediate B-4

1-Boc-4-[(1-pyrazolyl)acetyl]piperazine.

Prepared from pyrazole and 1-Boc-4-bromoacetylpiperazine using Method B-C.

1H-NMR

IS-MS, m/e 295.1 (M+1)

Preparation of Intermediates C-1 - C-11

The following compounds were prepared according to the indicated method (Method C-A, Method C-B or Method C-C) from the indicated starting materials, unless otherwise described.

Intermediate C-1

1-(Boc-D-phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]piperazine.

Method C-A

D-Boc-phenylglycine (8.4 g, 33.3 mmol) and

1-[2-(4-pyridinyl)ethyl]piperazine hydrochloride (10 g, 33.3 mmol) were dissolved in DMF (500 mL) and cooled to approximately -15 °C in an ice-methanol bath. Diethyl cyanophosphonate (5.5 mL, 36.6 mmol) was slowly added to the mixture. Triethylamine (18.6 mL, 133.2 mmol) was added dropwise to the solution. The mixture was stirred at -15 °C for 2 h and was allowed to gradually warm to room temperature overnight. The mixture was diluted with ethyl acetate and water. The layers were separated, and the water layer extracted with ethyl acetate. The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude product was filtered through a plug of silica gel (1.2 kg) using 1:1 hexanes:ethyl acetate as eluent to provide 1-(Boc-D-phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]piperazine (10.6 g, 75%) as a light yellow oil.

1H-NMR ($CDCl_3$)
CI-MS, m/e = 425 (M+1)

Intermediate C-2

1-(Boc-D-phenylglycinyl)-4-[2-(2-pyridinyl)ethyl]piperazine.

Prepared from Boc-D-phenylglycine and 1-[2-(2-pyridinyl)ethyl]piperazine using Method C-A.

1H-NMR($CDCl_3$)
CI-MS, m/e = 425 (M+1)

Intermediate C-3

1-(Boc-D-phenylglycinyl)-4-[2-(2-pyrazinyl)ethyl]piperazine.

Prepared from Boc-D-phenylglycine and 1-[2-(2-pyrazinyl)ethyl]piperazine using Method C-A.

1H-NMR($CDCl_3$)
CI-MS, m/e = 426 (M+1)

Intermediate C-4

1-(Boc-D-phenylglycinyl)-4-[2-(3-pyridazinyl)ethyl]piperazine.

Prepared from Boc-D-phenylglycine and 1-[2-(3-pyridazinyl)ethyl]piperazine using Method C-A.

1H NMR ($CDCl_3$)
TLC R_f=0.65 (100:10:1 CH_2Cl_2:MeOH:NH_4OH, SiO_2, Analtech No. 02521)

Intermediate C-5

1-(Boc-D-phenylglycinyl)-4-[2-(3-pyridinyl)ethyl]piperazine.

Prepared from Boc-D-phenylglycine and 1-[2-(3-pyridinyl)ethyl]piperazine using Method C-A.

1H-NMR($CDCl_3$)
CI-MS, m/e = 425 (M+1)

Intermediate C-6

1-(Boc-D-phenylglycinyl)-4-[2-(4-imidazolyl)ethyl]piperazine

Prepared from Boc-D-phenylglycine and 1-[2-(4-imidazolyl)ethyl]piperazine using Method C-A.

1H-NMR
IS-MS, m/e 414.2 (M+1)

Intermediate C-7

1-(Boc-D-phenylglycinyl)-4-[2-(4-pyrazolyl)ethyl]piperazine.

Prepared from Boc-D-phenylglycine and 1-[2-(4-pyrazolyl)ethyl]piperazine using Method C-A.

1H-NMR
IS-MS, m/e 414.2 (M+1)

Intermediate C-8

1-(Boc-D-phenylglycinyl)-4-[2-(1-imidazolyl)ethyl]piperazine.

Prepared from Boc-D-phenylglycine and 1-[2-(1-imid-

azolyl)ethyl]piperazine using Method C-A.

1H-NMR
IS-MS, m/e 414.2 (M+1)

Intermediate C-9

1-(Boc-D-phenylglycinyl)-4-[2-(1-pyrazolyl)ethyl]piperazine.

Prepared from Boc-D-phenylglycine and 1-[2-(1-pyrazolyl)ethyl]piperazine using Method C-A.

1H-NMR
IS-MS, m/e 414.2 (M+1)

Intermediate C-10

1-[Boc-D,L-(pyridin-2-yl)glycinyl]-4-[2-(4-pyridinyl)ethyl]-piperazine.

Method C-B

To a stirring solution of ethyl Boc-D,L-(pyridin-2-yl)-glycine (16.3 g, 58.2 mmol) in 1,4-dioxane (100 mL) was added a solution of LiOH hydrate (2.68 g, 64 mmol) in water (100 mL). After 2 h, another solution of LiOH hydrate (1.34 g, 32 mmol) in water (50 mL) was added. After another 2 h, the solvent was evaporated in vacuo to give 13.56 g of off-white solid.

A portion of the solid (3 g, 11.6 mmol) was dissolved in DMF (75 mL) and cooled to 0 °C. To this solution was added diethyl cyanophosphonate (2.3 g, 13.9 mmol), N,N-diisopropylethylamine (6 g, 46.4 mmol) and then 1-[2-(4-pyridyl)ethyl]piperazine hydrochloride (3.8 g, 12.8 mmol), and the reaction was allowed to slowly warm to room temperature overnight. The next morning, the solvents were removed in vacuo and the residue was dissolved in ethyl acetate and washed with satd aq. $NaHCO_3$ and brine, then dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was then dissolved in a minimal volume of dichloromethane and chromatographed over silica gel, eluting with a step gradient of 2% through 10% methanol (with 2 N NH_3) in dichloromethane.

The product containing fractions were combined and concentrated in vacuo to give 2.31 g (47%) of an off-white foam.

1H-NMR
IS-MS, m/e 426.3 (M+1)

Intermediate C-11

1-[Boc-D,L-(2-methoxyphenyl)glycinyl]-4-[2-(1-pyrazolyl)-ethyl]piperazine.

Method C-C

To a stirring solution of Boc-D,L-(2-methoxyphenyl)-glycine (2 g, 7.1 mmol) and 1-[2-(4-pyridinyl)ethyl]piperazine trihydrochloride (2.4 g, 7.8 mmol) in DMF (50 mL), was added HOBt (1.06 g, 7.8 mmol), and triethylamine (4.96 mL, 35.6 mmol) followed by DCC (1.61 g, 7.8 mmol). After stirring overnight at room temperature, the mixture was filtered; and the filtrate was concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with satd aq. $NaHCO_3$ followed by brine, then dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was then dissolved in a minimum amount of dichloromethane and chromatographed over silica gel, eluting with a step gradient of dichloromethane through 10% (2 N NH_3/methanol) in dichloromethane. The product containing fractions were combined and concentrated in vacuo to give 2.5 g (77%) of the title compound.

1H-NMR
IS-MS, m/e 455.1 (M+1)

Preparation of Intermediates D-1 - D-11

The following compounds were prepared according to the indicated method (Method D-A or Method D-B) from the indicated starting material, unless otherwise described.

Intermediate D-1

1-(D-Phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]piperazine

hydrochloride.

Method D-A

1-(Boc-D-phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]-piperazine (13 g, 30.6 mmol) and anisole (50 mL) were dissolved in methanol and cooled to 0 °C. Concentrated hydrochloric acid (40 mL, 300 mmol) was added dropwise to the solution, and the mixture allowed to warm to room temperature. The mixture stirred for 1 h, and the solvent and anisole were removed under vacuum. The residue was suspended in diethyl ether and sonicated for 1 h. The solid product was filtered and dried under vacuum (0.5 torr, 66 Pa at 50-60 °C) to give 1-(D-phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]piperazine hydrochloride (11.8 g, 89%) as a white, hygroscopic solid.

1H NMR (CD_3OD)
API-MS, m/e = 325 (M+1)

Intermediate D-2

1-(D-Phenylglycinyl)-4-[2-(2-pyridinyl)ethyl]piperazine.

Prepared from 1-(Boc-D-phenylglycinyl)-4-[2-(2-pyridinyl)ethyl]piperazine using Method D-A.

1H NMR (CD_3OD)
API-MS, m/e = 325 (M+1)

Intermediate D-3

1-(D-Phenylglycinyl)-4-[2-(2-pyrazinyl)ethyl]piperazine.

Prepared from 1-(Boc-D-phenylglycinyl)-4-[2-(2-pyrazinyl)ethyl]piperazine using Method D-A.

1H NMR (CD_3OD)
API-MS, m/e = 326 (M+1)

Intermediate D-4

1-(D-Phenylglycinyl)-4-[2-(3-pyridazinyl)ethyl]piperazine.

Prepared from 1-(Boc-D-phenylglycinyl)-4-[2-(3-pyridazinyl)ethyl]piperazine using Method D-A.

1H-NMR (CD_3OD)
IS-MS, m/e 326 (M+1)

Intermediate D-5

1-(D-Phenylglycinyl)-4-[2-(3-pyridinyl)ethyl]piperazine.

Prepared from 1-(Boc-D-phenylglycinyl)-4-[2-(3-pyridinyl)ethyl]piperazine using Method D-A.

1H NMR (CD_3OD)
API-MS, m/e = 325 (M+1)

Intermediate D-6

1-(D-Phenylglycinyl)-4-[2-(4-imidazolyl)ethyl]piperazine.

Prepared from 1-(Boc-D-phenylglycinyl)-4-[2-(4-imidazolyl)ethyl]piperazine using Method D-A.

1H-NMR
IS-MS, m/e 314.1 (M+1)

Intermediate D-7

1-(D-Phenylglycinyl)-4-[2-(4-pyrazolyl)ethyl]piperazine.

Prepared from 1-(Boc-D-phenylglycinyl)-4-[2-(4-pyrazolyl)ethyl]piperazine using Method D-A.

1H-NMR
IS-MS, m/e 314.3 (M+1)

Intermediate D-8

1-(D-Phenylglycinyl)-4-[2-(1-imidazolyl)ethyl]piperazine.

Prepared from 1-(Boc-D-phenylglycinyl)-4-[2-(1-imidazolyl)ethyl]piperazine using Method D-A.

1H-NMR
IS-MS, m/e 314.1 (M+1)

Intermediate D-9 (PD7-H7C-045, -046)

1-(D-Phenylglycinyl)-4-[2-(1-pyrazolyl)ethyl]piperazine.

Prepared from 1-(Boc-D-phenylglycinyl)-4-[2-(1-pyrazolyl)ethyl]piperazine using Method D-A.

1H-NMR
IS-MS, m/e 314.1 (M+1)

Intermediate D-10

1-[D,L-(Pyridin-2-yl)glycinyl]-4-[2-(4-pyridinyl)ethyl]-piperazine.

Method D-B

To a stirring solution of 1-[Boc-D,L-(pyridin-2-yl)-glycinyl]-4-[2-(4-pyridinyl)ethyl]piperazine (2.31 g, 5.4 mmol) in dichloromethane (45 mL) was added TFA (5 mL). After 6 h, the solvents were removed in vacuo. The residue was partitioned between ethyl acetate and satd aq. $NaHCO_3$, and the layers were separated. The aqueous phase was extracted with 50% ethyl acetate/dichloromethane, then 5% methanol/dichloromethane. The combined organic extracts were dried with $MgSO_4$, filtered and concentrated to give 1.66 g (94%) of the title compound.

1H-NMR
IS-MS, m/e 326.1 (M+1)

Intermediate D-11

1-[D,L-(2-Methoxyphenyl)glycinyl]-4-[2-(1-pyrazolyl)ethyl]-piperazine.

Prepared from 1-[Boc-D,L-(2-methoxyphenyl)glycinyl]-4-[2-(1-pyrazolyl)ethyl]piperazine using Method D-B.

1H-NMR
IS-MS, m/e 355.1 (M+1)

Preparation of Intermediates E

The following compounds were prepared according to the indicated method (Method E-A) from the indicated starting material, unless otherwise described.

Intermediate E-1

1-Boc-4-(Cbz-D-phenylglycinyl)piperazine.

Method E-A

D-Cbz-phenylglycine (58.0 g, 203 mmol) and 1-Boc-piperazine (41.7 g, 224 mmol) were dissolved in DMF (1 L) and cooled to approximately -15 °C in an ice-methanol bath. Diethyl cyanophosphonate (37.0 mL, 244 mmol) was slowly added to the mixture. Triethylamine (59.4 mL, 426 mmol) was added dropwise to the solution. The mixture was stirred at -15 °C for 2 h and was allowed to gradually warm to room temperature overnight. The mixture was diluted with ethyl acetate and water. The layers were separated, and the water layer extracted with ethyl acetate. The organic layers were combined, washed with 10% citric acid (2 x 500 mL) and brine, dried (Na_2SO_4), filtered and concentrated under vacuum. The crude product was filtered through a plug of silica gel (1.2 kg) using 1:1 hexanes:ethyl acetate as eluent to provide 1-Boc-4-(Cbz-D-phenylglycinyl)piperazine (69.9 g, 76%) as a colorless oil.

1H-NMR($CDCl_3$)
API-MS, m/e = 454 (M+1)

Preparation of Intermediates F

The following compounds were prepared according to the indicated method (Method F-A) from the indicated starting material, unless otherwise described.

Intermediate F-1

1-Boc-4-(D-phenylglycinyl)piperazine.

Method F-A

1-Boc-4-(Cbz-D-phenylglycinyl)piperazine (69.5 g, 153

mmol) was dissolved in ethanol (500 mL). The mixture was degassed with nitrogen and 10% Pd/C (6.8 g) was added. Hydrogen was bubbled through the mixture for 1 h, and it was maintained under a hydrogen atmosphere for 16 h. The Pd/C was removed by filtration through cellulose. The filter cake was rinsed with ethanol and ethyl acetate. The filtrate was concentrated under vacuum to give 1-Boc-4-(D-phenylglycinyl)piperazine (45.3 g, 93%) as a light yellow solid.

1H-NMR($CDCl_3$)
API-MS, m/e = 320 (M+1)

Preparation of Intermediates G

The following compounds were prepared according to the indicated method (Method G-A) from the indicated starting material, unless otherwise described.

Intermediate G-1

1-Boc-4-(4-Methoxybenzoyl-D-phenylglycinyl)piperazine.

Method G-A

1-Boc-4-(D-phenylglycinyl)piperazine (42.0 g, 131.5 mmol) was dissolved in 1,4-dioxane (420 mL) and water (210 mL) and was cooled to 10 °C. Potassium carbonate (36.4 g, 263 mmol) was added, followed by *p*-methoxybenzoyl chloride (24.7 g, 144 mmol). The mixture stirred at room temperature overnight. The mixture was diluted with water and ethyl acetate. The layers were separated and the water layer extracted with ethyl acetate. The organic layers were combined, washed with brine, dried, filtered and concentrated to provide 1-Boc-4-(4-methoxybenzoyl-D-phenylglycinyl)piperazine (58.7 g, 98%) as an off-white solid.

1H-NMR($CDCl_3$)
API-MS, m/e = 454 (M+1)

Preparation of Intermediates H

The following compounds were prepared according to the indicated method (Method H-A) from the indicated starting material, unless otherwise described.

Intermediate H-1

1-(4-Methoxybenzoyl-D-phenylglycinyl)piperazine trifluoroacetate.

Method H-A

1-Boc-4-(4-Methoxybenzoyl-D-phenylglycinyl)piperazine (20.0 g, 44.1 mmol) was dissolved in dichloromethane (50 mL) and anisole (20 mL). To this vigorously stirred mixture was added trifluoroacetic acid (50 mL). The mixture was stirred for 25 min at room temperature. The solvents were removed under vacuum. The residue was triturated in ether and sonicated for 60 min. The solid was collected by filtration and dried in a vacuum pistol overnight to provide 1-(4-methoxybenzoyl-D-phenylglycinyl)piperazine trifluoroacetate (18.2 g, 88%) as a light yellow solid.

1H-NMR(CD_3OD)
API-MS, m/e = 354 (M+1)

Preparation of Examples 1 - 55

The following examples of formula (I) were prepared according to the indicated method (Method I-A, Method I-B, Method I-C, Method I-D or Method I-E) from the indicated starting materials, unless otherwise described.

Example 1

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-phenethylpiperazine.

Method I-A

To a stirring solution of 1-(4-methoxybenzoyl-D-phenylglycinyl)piperazine (0.05 g, 0.14 mmol) in methanol (1 mL) was added phenylacetaldehyde (0.17 mL, 1.4 mmol), followed by acetic acid (0.05 mL, 0.87 mmol) and then sodium cyanoborohydride (0.014 g, 0.21 mmol). After 2 h, the

solution was loaded onto an SCX column, which was pretreated with 5% acetic acid/methanol. The column was washed with methanol and then the product was eluted with 10/1 dichloromethane:(2 N NH_3 in methanol). The product containing fractions were combined and concentrated to give 63 mg of thick oil (90% pure by analytical HPLC). The crude product was dissolved in a minimal volume of dichloromethane and chromatographed over silica gel, eluting with dichloromethane, followed by ethyl acetate, followed by a gradient of 2% through 10% (2 N NH_3/methanol) in dichloromethane. The product containing fractions were combined and concentrated to give 0.022 g (34%) of the title compound.

1H-NMR
IS-MS, m/e 458.0 (M+1)
HPLC Analysis (Method A): 100% t_r = 27.44 min.

Example 2

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-[2-(4-pyridinyl)-ethyl]piperazine Hydrochloride.

Method I-B

1-(D-Phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]piperazine trihydrochloride (1.0 g, 2.31 mmol) and potassium carbonate (2.0 g, 144.4 mmol) were dissolved in 1,4-dioxane (5 mL) and water (1 mL). To this solution, p-anisoyl chloride (650 μL, 4.62 mmol) was added. The mixture stirred at room temperature for 3 h. The mixture was diluted with water, and the mixture extracted with ethyl acetate. The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was dissolved in methanol and loaded onto an SCX column (10 g, pretreated with 5% acetic acid in methanol and washed with methanol). The by-products were eluted with methanol (about 20 mL), and desired product eluted with saturated ammonia in methanol. The product was further purified by column chromatography (SiO_2, CH_2Cl_2:CMA 20:1 to 9:1 gradient). The product was dissolved in methanol, and HCl in diethyl ether was added to provide 1-(4-methoxybenzoyl-D-phenylglycinyl)-4-[2-(4-

pyridinyl)ethyl]piperazine hydrochloride (370 mg, 37%) as an off white solid.

1H-NMR($CDCl_3$)
CI-MS, m/e = 459 (M+1)
Analysis for $C_{27}H_{30}N_4O_3 \cdot 2.2HCl \cdot 1.1H_2O \cdot 0.4NH_4Cl$:
Calcd: C, 55.91; H, 6.26; N, 10.63;
Found: C, 56.04; H, 6.55; N, 10.46.
HPLC Analysis (Method B): 99.7%, t_R = 10.98 min.

Example 3

1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[2-(4-pyridinyl)-ethyl]piperazine.

Method I-C

1-(D-Phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]piperazine (1.0 g, 2.31 mmol), 6-carboxyindole (371 mg, 2.31 mmol), HOBt (312 mg, 2.31 mmol), Et_3N (1.3 mL, 9.24 mmol), and DCC (620 mg, 3.00 mmol) were stirred in DMF at room temperature overnight. The precipitate was removed by filtration, and the filtrate concentrated under vacuum to a thick paste. The residue was dissolved in methanol and purified by ion exchange chromatography (SCX resin, methanol then saturated NH_3 in methanol) to provide the crude product as a brown solid. The crude product was purified by chromatography (SiO_2, 20:1 CH_2Cl_2:CMA to 6:1 CH_2Cl_2:CMA) to provide 1-(indole-6-carbonyl-D-phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]piperazine (350 mg, 32%) as an off white solid.

Melting Point = 75-80 °C
IR (thin film)
1H NMR ($CDCl_3$)
Analysis for $C_{28}H_{29}N_4O_3$:
Calcd: C, 50.12; H, 5.06; N, 7.54;
Found: C, 49.81; H, 5.33; N, 7.39.
HPLC Analysis (Method B): >99% t_r = 12.4 min.

Example 3a

1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[2-(4-pyridinyl)-ethyl]piperazine Dihydrochloride.

Prepared from 1-(indole-6-carbonyl-D-phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]piperazine using Method I-D (but using dichloromethane as the initial solvent).

1H NMR
IS-MS, m/e 468.2 (M+1)
Analysis for $C_{28}H_{29}N_5O_2 \cdot 1.9HCl \cdot 2.0H_2O$:
Calcd: C, 58.70; H, 6.14; N, 12.22; Cl, 11.76;
Found: C, 58.86; H, 5.62; N, 12.07; Cl, 11.78.
HPLC Analysis (Method A): 100 % t_r = 19.24 min.

Example 4

1-(3-Chloroindole-6-carbonyl-D-phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]piperazine.

Prepared from 3-chloroindole-6-carboxylic acid and 1-(D-phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]piperazine using Method I-C.

Melting point = 100-105 °C
1H-NMR ($CDCl_3$)
API-MS, m/e = 502 (M+1)
Analysis for $C_{28}H_{28}ClN_5O_2 \cdot 1.2H_2O$:
Calcd: C, 64.23; H, 5.85; N, 13.37;
Found: C, 64.38; H, 5.74; N, 13.22.
HPLC Analysis (Method B): 97.2% t_r = 13.8 min.

Example 4a

1-(3-Chloroindole-6-carbonyl-D-phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]piperazine Dihydrochloride.

Prepared from 1-(3-chloroindole-6-carbonyl-D-phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]piperazine using Method I-D (but using dichloromethane as the initial solvent).

1H NMR
IS-MS, m/e 502.1 (M+1)
Analysis for $C_{28}H_{28}ClN_5O_2 \cdot 2.0HCl \cdot 1.8H_2O$:
Calcd: C, 55.37; H, 5.58; N, 11.53; Cl, 17.51;
Found: C, 55.03; H, 5.34; N, 11.30; Cl, 17.26.
HPLC Analysis (Method A): 100 % t_r = 24.55 min.

Example 5

1-(5-Chloroindole-2-carbonyl-D-phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]piperazine.

Prepared from 5-chloroindole-2-carboxylic acid and 1-(D-phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]piperazine using Method I-C.

Melting Point = 106-110 °C
IR (thin film)
1H-NMR ($CDCl_3$)
API-MS, m/e = 502 (M+1)
HPLC Analysis (Method B): 88.7% t_r = 14.9 min.

Example 6

1-(Indole-2-carbonyl-D-phenylglycinyl)-4-[2-(4-pyridinyl)-ethyl]piperazine.

Prepared from indole-2-carboxylic acid and 1-(D-phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]piperazine using Method I-C.

Melting point = 95-100 °C
1H-NMR ($CDCl_3$)
IR (thin film)
API-MS, m/e 468 (M+1)
Analysis for $C_{28}H_{29}N_5O_2 \cdot 1.7H_2O$:
Calcd: C, 67.51; H, 6.55; N, 14.06;
Found: C, 67.00; H, 6.10; N, 14.02.

HPLC Analysis (Method B): 96.5% t_r = 13.5 min.

Example 7

1-(3-Methylindole-6-carbonyl-D-phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]piperazine.

Prepared from 3-methylindole-6-carboxylic acid and 1-(D-phenylglycinyl)-4-[2-(4-pyridinyl)ethyl]piperazine using Method I-C.

Melting point = 62-65 °C
1H-NMR ($CDCl_3$)
IR (thin film)
API-MS, m/e 482 (M+1)
Analysis for $C_{29}H_{31}N_5O_2 \cdot 1.6H_2O$:
Calcd: C, 68.24; H, 6.75; N, 13.72;
Found: C, 68.25; H, 6.66; N, 13.78.
HPLC Analysis (Method B): 93.6% t_r = 13.3 min.

Example 8

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-[2-(2-pyridinyl)-ethyl]piperazine.

Prepared from 4-methoxybenzoyl chloride and 1-(D-phenylglycinyl)-4-[2-(2-pyridinyl)ethyl]piperazine using Method I-B.

Melting point = 168-180 °C
$[\alpha]^{25}{}_D$ -87.7 (*c* 1.00, methanol)
1H-NMR (CD_3OD)
CI-MS, m/e = 459 (M+1)
Analysis for $C_{27}H_{30}N_4O_2 \cdot 2.0HCl \cdot 0.9H_2O$:
Calcd: C, 59.21; H, 6.22; N, 10.23; Cl, 12.95,
Found: C, 58.88; H, 6.25; N, 10.19; Cl, 13.26.
HPLC Analysis (Method B): 97.5% t_r = 12.2 min.

Example 9

1-(3-Chloroindole-6-carbonyl-D-phenylglycinyl)-

4-[2-(2-pyridinyl)ethyl]piperazine.

Prepared from 3-chloroindole-6-carboxylic acid and 1-(D-phenylglycinyl)-4-[2-(2-pyridinyl)ethyl]piperazine using Method I-C.

Melting point = 93-96 °C
$[\alpha]^{25}_D$ -72.4 (*c* 0.61, chloroform)
1H-NMR ($CDCl_3$)
CI-MS, m/e = 502 (M+1)
Analysis for $C_{28}H_{28}N_5O_2 \cdot 0.4H_2O$:
Calcd: C, 66.04; H, 5.07; N, 13.75; Cl, 6.96;
Found: C, 65.94; H, 5.61; N, 13.74; Cl, 6.91.
HPLC Analysis (Method B): 98.3% t_r = 14.1 min.

Example 10

1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[2-(2-pyridinyl)-ethyl]piperazine.

Prepared from indole-6-carboxylic acid and 1-(D-phenylglycinyl)-4-[2-(2-pyridinyl)ethyl]piperazine using Method I-C.

Melting point = 73-78 °C
$[\alpha]^{25}_D$ -90.9 (*c* 0.25, chloroform)
1H-NMR ($CDCl_3$)
CI-MS, m/e = 468 (M+1)
Analysis for $C_{28}H_{28}N_5O_2 \cdot 0.6H_2O$:
Calcd: C, 70.30; H, 6.36; N, 14.64;
Found: C, 70.39; H, 6.30; N, 14.62.
HPLC Analysis (Method B): 98.3% t_r = 14.1 min.

Example 11

1-[4-Methoxybenzoyl-D,L-(pyridin-2-yl)glycinyl]-4-[2-(4-pyridinyl)ethyl]piperazine.

Prepared from 4-methoxybenzoic acid and 1-[D,L-(pyridin-2-yl)glycinyl]-4-[2-(4-pyridinyl)ethyl]piperazine using Method I-C.

1H-NMR

IS-MS, m/e 460.3 (M+1)

Analysis for $C_{26}H_{29}N_5O_3 \cdot 3.5HCl \cdot 4H_2O$:

Calcd: C, 47.37; H, 6.19; N, 10.62;

Found: C, 47.17; H, 5.75; N, 10.56.

HPLC Analysis (Method A): 100% t_r = 10.48 min.

Example 12

1-[3-Chloroindole-6-carbonyl-D,L-(pyridin-2-yl)glycinyl]-4-[2-(4-pyridinyl)ethyl]piperazine.

Prepared from 3-chloroindole-6-carboxylic acid and 1-[D,L-(pyridin-2-yl)glycinyl]-4-[2-(4-pyridinyl)ethyl]-piperazine using Method I-C.

1H-NMR

IS-MS, m/e 503.5 (M+1)

Analysis for $C_{27}H_{27}N_6O_2Cl \cdot 3HCl \cdot 5H_2O$:

Calcd: C, 46.16; H, 5.74; N, 11.96; Cl, 20.19;

Found: C, 46.10; H, 5.59; N, 11.68; Cl, 20.29.

HPLC Analysis (Method A): 99% t_r = 18.64 min.

Example 13

1-[3-Methylindole-6-carbonyl-D,L-(pyridin-2-yl)glycinyl]-4-[2-(4-pyridinyl)ethyl]piperazine.

Prepared from 3-methylindole-6-carboxylic acid and 1-[D,L-(pyridin-2-yl)glycinyl]-4-[2-(4-pyridinyl)ethyl]-piperazine using Method I-C.

1H-NMR

IS-MS, m/e 483.5 (M+1)

HPLC Analysis (Method A): 99% t_r = 16.14 min.

Example 14

1-[Indole-6-carbonyl-D,L-(pyridin-2-yl)glycinyl]-4-[2-(4-pyridinyl)ethyl]piperazine.

Prepared from indole-6-carboxylic acid and 1-[D,L-

(pyridin-2-yl)glycinyl]-4-[2-(4-pyridinyl)ethyl]piperazine using Method I-C.

1H-NMR
IS-MS, m/e 469.3 (M+1)
HPLC Analysis (Method A): 100% t_r = 12.87 min.

Example 15

1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[2-(3-pyridinyl)-ethyl]piperazine.

Prepared from indole-6-carboxylic acid and 1-(D-phenylglycinyl)-4-[2-(3-pyridinyl)ethyl]piperazine using Method I-C.

Melting point = 82-87 °C
$[\alpha]^{25}_D$ -116.0 (*c* 0.25, methanol)
IR (thin film)
1H-NMR ($CDCl_3$)
API-MS, m/e = 468 (M+1)
Analysis for $C_{28}H_{29}N_5O_2 \cdot 1.25H_2O$:
Calcd: C, 68.62; H, 6.48; N, 14.29;
Found: C, 68.49; H, 6.39; N, 14.13.
HPLC Analysis (Method B): >99% t_r = 12.3 min.

Example 16

1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[2-(2-pyrazinyl)-ethyl]piperazine.

Prepared from indole-6-carboxylic acid and 1-(D-phenylglycinyl)-4-[2-(2-pyrazinyl)ethyl]piperazine using Method I-C.

Melting Point = 53-58 °C
$[\alpha]^{25}_D$ -91.4 (*c* 0.23, chloroform)
1H-NMR ($CDCl_3$)
IR (thin film)
API-MS, m/e 469 (M+1)
Analysis for $C_{27}H_{28}N_6O_2 \cdot 1.6H_2O$:
Calcd: C, 65.20; H, 6.32; N, 16.90;
Found: C, 65.49; H, 6.02; N, 16.54.

HPLC Analysis (Method B): 98.5% t_r = 13.6 min.

Example 17

1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[2-(1-imidazolyl)-ethyl]piperazine.

Prepared from indole-6-carboxylic acid and 1-(D-phenylglycinyl)-4-[2-(1-imidazolyl)ethyl]piperazine using Method I-C.

1H-NMR
IS-MS, m/e 457.3 (M+1)
Analysis for $C_{26}H_{28}N_6O_2 \cdot 1.1H_2O$:
Calcd: C, 65.55; H, 6.39; N, 17.64;
Found: C, 66.01; H, 6.23; N, 17.14.
HPLC Analysis (Method A): 99% t_r = 19.66 min.

Example 18

1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[2-(1-pyrazolyl)-ethyl]piperazine.

Prepared from indole-6-carboxylic acid and 1-(D-phenylglycinyl)-4-[2-(1-pyrazolyl)ethyl]piperazine using Method I-C.

1H-NMR
IS-MS, m/e 457.2 (M+1)
Analysis for $C_{26}H_{28}N_6O_2 \cdot 1.3H_2O$:
Calcd: C, 65.06; H, 6.43; N, 17.51;
Found: C, 65.39; H, 6.53; N, 16.98.
HPLC Analysis (Method A):>97% t_r = 22.98 min.

Example 19

1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[2-(4-imidazolyl)-ethyl]piperazine.

Prepared from indole-6-carboxylic acid and 1-(D-phenylglycinyl)-4-[2-(4-imidazolyl)ethyl]piperazine using Method I-C.

1H-NMR

IS-MS, m/e 457.3 (M+1)

Analysis for $C_{26}H_{28}N_6O_2 \cdot 2.1HCl \cdot 4.0H_2O$:

Calcd: C, 51.60; H, 6.35; N, 13.89; Cl, 12.30;

Found: C, 51.82; H, 6.04; N, 13.56; Cl, 12.12.

HPLC Analysis (Method A): 94% t_r = 17.78 min.

Example 20

1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[2-(4-pyrazolyl)-ethyl]piperazine.

Prepared from indole-6-carboxylic acid and 1-(D-phenylglycinyl)-4-[2-(4-pyrazolyl)ethyl]piperazine using Method I-C.

1H-NMR

IS-MS, m/e 457.3 (M+1)

Analysis for $C_{26}H_{28}N_6O_2 \cdot 1.3HCl \cdot 1.75H_2O$:

Calcd: C, 58.32; H, 6.17; N, 15.70; Cl, 8.61;

Found: C, 58.31; H, 5.72; N, 15.48; Cl, 8.37.

HPLC Analysis (Method A): >98% t_r = 19.95 min.

Example 21

1-(Indole-6-carbonyl-D-phenylglycinyl)-4-[2-(3-pyridazinyl)-ethyl]piperazine.

Prepared from indole-6-carboxylic acid and 1-(D-phenylglycinyl)-4-[2-(3-pyridazinyl)ethyl]piperazine using Method I-C.

Melting Point = 219-222 °C with decomposition

1H NMR ($CDCl_3$)

$[\alpha]^{25}_D$ -53.9° (*c* 0.25, dimethyl sulfoxide)

API-MS, m/e = 469 (M+1)

HPLC Analysis (Method B): >99% t_r = 12.8 min.

Example 22

1-[4-Methoxybenzoyl-D,L-(2-methoxyphenyl)glycinyl]-4-[2-(4-pyridinyl)ethyl]piperazine.

Prepared from 4-methoxybenzoic acid and 1-[D,L-(2-meth-

oxyphenyl)glycinyl]-4-[2-(4-pyridinyl)ethyl]piperazine using Method I-C.

1H-NMR
IS-MS, m/e 489.1 (M+1)
Analysis for $C_{28}H_{32}N_4O_4 \cdot 0.5H_2O$:
Calcd: C, 67.59; H, 6.68; N, 11.26;
Found: C, 67.57; H, 6.49; N, 11.11.
HPLC Analysis (Method A): 97.2% t_r = 16.02 min.

Example 23

1-[Indole-6-carbonyl-D,L-(2-methoxyphenyl)glycinyl]-4-[2-(4-pyridinyl)ethyl]piperazine hydrochloride.

Prepared from indole-6-carboxylic acid and 1-[D,L-(2-methoxyphenyl)glycinyl]-4-[2-(4-pyridinyl)ethyl]piperazine using Method I-C, followed by Method I-D.

1H-NMR
IS-MS, m/e 498.0 (M+1)
Analysis for $C_{29}H_{31}N_5O_3 \cdot 2.1HCl \cdot 2.5H_2O$:
Calcd: C, 56.25; H, 6.20; N, 11.31; Cl, 12.02;
Found: C, 56.56; H, 5.83; N, 11.21; Cl, 12.13.
HPLC Analysis (Method A): 100% t_r = 17.24 min.

Examples 24 - 25

The compounds of Examples 24 and 25 were prepared by coupling Boc-D-4-carboxamidophenylglycine to the appropriate amine with EDCI/HOAt (similar to Method C-C), deprotection with TFA/DCM (similar to Method D-B) and coupling to 3-amino-4-chlorobenzoic acid with EDCI/HOAt (similar to Method I-C).

Example 24

1-[3-Amino-4-chlorobenzoyl-D-(4-carboxamidophenyl)glycinyl]-4-(2-phenylethyl)piperazine.

Hplc (Method C) rt 11.1min.
LCMS M+1 521. Nmr.

Example 25

1-[3-Amino-4-chlorobenzoyl-D-4-carboxamidophenylglycinyl)-4-benzylpiperazine.

Hplc (Method C) rt 11.4min.
LCMS M+1 512. Nmr.

Example 26

1-[Indole-6-carbonyl-D-(4-carboxyphenyl)glycinyl]-4-(1-methylpiperidin-4-yl)piperazine.

By coupling of Boc-D-4-carboxymethylphenylglycine with 1-(1-methylpiperidin-4-yl)piperazine using HOAt and EDCI (similar to Method C-C), followed by TFA deprotection (similar to Method D-B), coupling to indole-6-carboxylic acid using HOAt and EDCI (similar to Method I-C) followed by hydrolysis of the methyl ester with lithium hydroxide.
Hplc (Method C) rt, 6.05min
LCMS M+1 504
Nmr.

Example 27

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(4-piperidinyl-methyl)piperazine Trifluoroacetate.

Preparation of Starting Materials

1-Boc-isonipecotic acid

Isonipecotic acid (15.0 g, 116 mmol) was dissolved in THF (300 mL), water (150 mL) and 6 N NaOH (40 mL). Di-*tert*-butyl dicarbonate (26.6 g, 122 mmol) was added and the mixture stirred overnight. The mixture was diluted with water and ethyl acetate, and the layers separated. The water layers were extracted with ethyl acetate, and the organic layers discarded. The water layer was diluted with $KHSO_4$ (2 N, pH~4) and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated

to provide 1-Boc-isonipecotic acid (23.9 g, 90%) as a white solid.
1H-NMR($CDCl_3$)
API-MS, m/e = 230 (M+1)

1-Boc-piperidine-4-methanol

1-Boc-isonipecotic acid (10.0 g, 214 mmol) was dissolved in THF (400 mL) and cooled to 0 °C. A solution of $BH_3 \cdot THF$ (180 mL, 1 N in THF, 180 mmol) was added slowly. The mixture stirred for 1 h at 0 °C and was allowed to warm to room temperature for 12 h. The mixture was carefully quenched with water and diluted with ethyl acetate. The water layer was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried (Na_2SO_4), filtered and concentrated to provide 1-Boc-piperidine-4-methanol (7.98 g, 85%) as a white solid.
1H-NMR($CDCl_3$)
API-MS, m/e = 220 (M+1)

1-Boc-piperidine-4-carboxaldehyde.

Dimethyl sulfoxide (3.5 mL, 48.7 mmol) was dissolved in dichloromethane (100 mL) and was cooled to -78 °C. Oxalyl chloride (3.65 mL, 41.8 mmol) was added. The mixture stirred for 30 min. To this solution was added a solution of 1-Boc-piperidine-4-methanol (7.5 g, 34.8 mmol) in dichloromethane (15 mL), and the mixture stirred for 1 h. Triethylamine (9.7 mL, 69.6 mmol) was added slowly and the mixture stirred at -78 °C for 30 min and warmed to room temperature over the course of 1 h. The mixture was diluted with water and the layers separated. The water layer was extracted with dichloromethane and the organic layers combined, dried (Na_2SO_4), filtered and concentrated to provide 1-Boc-piperidine-4-carboxaldehyde (6.75 g, 91%) as a yellow oil.
1H-NMR($CDCl_3$)
API-MS, m/e = 214 (M+1)

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(1-Boc-piperidin-4-ylmethyl)piperazine

Prepared from 1-(4-methoxybenzoyl-D-phenylglycinyl)piperazine trifluoroacetate and 1-Boc-piperidine-4-carboxaldehyde using Method I-A (but using sodium triacetoxyborohydride in 1,2-dichloroethane) (85%).
1H-NMR($CDCl_3$)

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(4-piperidinyl-methyl)piperazine trifluoroacetate.

Prepared from 1-(4-methoxybenzoyl-D-phenylglycinyl)-4-(1-Boc-piperidin-4-ylmethyl)piperazine using Method H-A (90%).
Melting Point = 70-72 °C with decomposition
IR(KBr)
1H-NMR(CD_3OD)
API-MS, m/e = 451 (M+1)
Analysis for $C_{26}H_{34}N_4O_3 \cdot 2.5TFA \cdot 0.4H_2O$:
Calcd: C, 50.12; H, 5.06; N, 7.54;
Found: C, 49.81; H, 5.33; N, 7.39.
HPLC Analysis (Method B): 97.1% RT=14.3 min.

Examples 28 - 29

Unless otherwise indicated, using Method I-A, the title compounds were prepared from 1-(4-methoxybenzoyl-D-phenylglycinyl)-4-(4-piperidinylmethyl)piperazine trifluoroacetate and the indicated aldehyde or ketone.

Example 28

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(1-methylpiperidin-4-ylmethyl)piperazine.

Prepared from paraformaldehyde (56%).
IR (KBr)
1H-NMR(CD_3OD)
CI-MS, m/e = 465 (M+1)

Example 29

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(1-isopropyl-piperidin-4-ylmethyl)piperazine Hydrochloride.

Prepared from acetone using Method I-A, followed by Method I-D (but using methanol in place of ether/dichloromethane) (72%).

Melting Point = 172-180 °C with decomposition

IR (KBr)

1H-NMR(CD_3OD)

CI-MS, m/e = 493 (M+1)

Analysis for $C_{29}H_{40}N_4O_3 \cdot 3HCl$:

Calcd: C, 55.85; H, 7.34; N, 8.98;

Found: C, 55.63; H, 7.32; N, 8.66.

HPLC Analysis (Method B): 98.2% RT=14.4 min.

Example 30

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(2-cyclopentyl-ethyl)piperazine

Preparation of Starting Materials:

Cyclopentylacetaldehyde

Prepared from 2-cyclopentylethanol using the Dess-Martin oxidation (Dess, D. B.; Martin, J. C.; J. Am. Chem. Soc., 1991, *113*, 7277). The aldehyde was used with trace amounts of ether and methylene chloride present due to volatility of product.

1H NMR ($CDCl_3$)

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(2-cyclopentyl-ethyl)piperazine

Prepared from cyclopentylacetaldehyde using Method I-A (58%).

1H NMR ($CDCl_3$)

Example 30A

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(2-cyclopentyl-ethyl)piperazine Hydrochloride Hydrate

Method I-D

To a stirred solution of 1-(4-methoxybenzyl-D-phenylglycinyl)-4-(2-cyclopentylethyl)piperazine (260 mg, 0.58 mmol) in ether (10 mL) and methylene chloride (1 mL) was added hydrogen chloride as a 2 N solution in ether (about 2 mL), and the resulting precipitate was filtered to give 1-(4-methoxybenzoyl-D-phenylglycinyl)-4-(2-cyclopentylethyl)piperazine hydrochloride as a pale yellow solid.

1H NMR (CD_3OD)

IS-MS, m/e = 450 (M+1)

Analysis for $C_{27}H_{35}N_3O_3 \cdot HCl \cdot 0.5H_2O$:

Calcd: C, 65.51; H, 7.53; N, 8.49;

Found: C, 65.67; H, 7.58; N, 8.13.

HPLC Analysis (Method D): >99%, RT=15.84

Melting Point = 190-192 °C

Example 31

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(3-pyrrolidinyl)-piperazine Trifluoroacetate.

Preparation of Starting Materials

(R)-(+)-1-Boc-3-pyrrolidinol

To a stirred solution of (R)-(+)-3-pyrrolidinol (2 g, 22.96 mmol) in tetrahydrofuran (60 mL) and water (30 mL) was added di-*tert*-butyl dicarbonate (5.27 g, 24.15 mmol) and 3 N sodium hydroxide (16 mL), and the resulting solution was stirred for 6 h. Another portion of di-*tert*-butyl dicarbonate (0.74 g, 0.34 mmol) was added and the solution was stirred overnight. The reaction was diluted with water (40 mL) and extracted with ethyl acetate (2 x 150 mL). The combined organic extracts were washed with 2 N potassium hydrogen sulfate (200 mL), saturated sodium bicarbonate (2 x 150 mL), brine (150 mL) and dried over magnesium sulfate. Removal of solvent *in vacuo* gave (R)-(+)-1-Boc-3-pyrrolidinol (4.21 g, 98%) as a yellow oil.

1H-NMR ($CDCl_3$)

1-Boc-3-pyrrolidinone

Prepared from (R)-(+)-1-Boc-3-pyrrolidinol using the Dess-Martin oxidation (Dess, D. B.; Martin, J. C.; J. Am. Chem. Soc., **1991**, *113*, 7277)(85%).

1H NMR ($CDCl_3$)

1-(4-Methoxybenzyl-D-phenylglycinyl)-4-(1-Boc-3-pyrrolidinyl)piperazine

Prepared from 1-(4-methoxybenzyl-D-phenylglycinyl)piperazine trifluoroacetate and 1-Boc-3-pyrrolidinone using Method I-A (69%).

1H NMR ($CDCl_3$)

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(3-pyrrolidinyl)-piperazine trifluoroacetate.

Prepared from 1-(4-methoxybenzyl-D-phenylglycinyl)-4-(1-Boc-3-pyrrolidinyl)piperazine using Method H-A.

1H NMR (CD_3OD)

Examples 32 - 33

Using Method I-A (but using NaBH(OAc)3 in 1,2-dichloroethane), the title compounds were prepared from 1-(4-methoxybenzoyl-D-phenylglycinyl)-4-(3-pyrrolidinyl)piperazine trifluoroacetate and the indicated aldehyde or ketone.

Example 32

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(1-methylpyrrolidin-3-yl)piperazine.

Prepared from paraformaldehyde (20%).

1H-NMR($CDCl_3$)

Example 33

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(1-isopropyl-pyrrolidin-3-yl)piperazine.

Prepared from acetone (59%).

1H-NMR($CDCl_3$)

Examples 34 - 50 {304 to 314}

Unless otherwise indicated, the products of Examples 34-50 were obtained from 1-(4-methoxybenzoyl-D-phenylglycinyl)piperazine and the indicated aldehyde or ketone using Method I-A.

Example 34

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(2-pyridylmethyl)-piperazine.

Prepared from 2-pyridinecarboxaldehyde (48%).
1H-NMR
IS-MS, m/e 444.9 (M+1)
Analytical RPHPLC, Method A, RT = 21.70 min (100%)

Example 35

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(3-pyridylmethyl)-piperazine.

Prepared from 3-pyridinecarboxaldehyde (42%).
1H-NMR
IS-MS, m/e 444.9 (M+1)
Analytical RPHPLC, Method A, RT = 17.84 min (99%)

Example 36

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(4-pyridylmethyl)-piperazine.

Prepared from 4-pyridinecarboxaldehyde (45%).
1H-NMR
IS-MS, m/e 444.9 (M+1)
Analytical RPHPLC, Method A, RT = 18.36 min (99%)

Example 37

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(3-pentyl)piperazine.

Prepared from 3-pentanone (88%).
1H-NMR

IS-MS, m/e 424.0 (M+1)
Analytical RPHPLC, Method A, RT = 23.62 min (100%)

Example 38

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-cyclopentylpiperazine.
Prepared from cyclopentanone (95%).
1H-NMR
IS-MS, m/e 422.0 (M+1)
Analytical RPHPLC, Method A, RT = 20.76 min (100%)

Example 39

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(4-methylcyclohexyl)piperazine.
Prepared from 4-methylcyclohexanone (46%).
1H-NMR
IS-MS, m/e 450.0 (M+1)
Analytical RPHPLC, Method A, RT = 27.07 min (isomer 1), 27.74 min (isomer 2).

Example 40

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(tetrahydrothiopyran-4-yl)piperazine.
Prepared from tetrahydro-4H-thiopyran-4-one (86%).
1H-NMR
IS-MS, m/e 453.9 (M+1)
Analytical RPHPLC, Method A, RT = 22.96 min (100%)

Example 41

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(2-indanyl)piperazine.
Prepared from 2-indanone (92%).
1H-NMR
IS-MS, m/e 469.9 (M+1)
Analytical RPHPLC, Method A, RT = 26.32 min (100%)

Example 42

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-benzylpiperazine.

Prepared from benzaldehyde (87%).
1H-NMR
IS-MS, m/e 444.0 (M+1)
Analytical RPHPLC, Method A, RT = 25.78 min (96%)

Example 43

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(cyclohexyl-methyl)piperazine.

Prepared from cyclohexanecarboxaldehyde (86%).
1H-NMR
IS-MS, m/e 450.2 (M+1)
Analytical RPHPLC, Method A, RT = 28.07 min (94%)

Example 44

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(4-heptyl)piperazine.

Prepared from 4-heptanone (89%).
1H-NMR
IS-MS, m/e 452.0 (M+1)
Analytical RPHPLC, Method A, RT = 29.62 min (94%)

Example 45

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(4-pyranyl)piperazine.

Prepared from pyran-4-one (95%).
1H-NMR
IS-MS, m/e 437.9 (M+1)
Analytical RPHPLC, Method A, RT = 18.46 min (97.5%)

Example 46

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-cyclohexylpiperazine.

Prepared from cyclohexanone (quantitative).
1H-NMR
IS-MS, m/e 436.0 (M+1)
Analytical RPHPLC, Method A, RT = 23.43 min (100%)

Examples 47 - 50

Preparation of Starting Materials

1-(Cbz-D-phenylglycinyl)piperazine.

Prepared from 1-(Cbz-D-phenylglycinyl)-4-Boc-piperazine using Method H-A. The crude product was dissolved in ethyl acetate and washed with satd aq. $NaHCO_3$, followed by brine, then dried with $MgSO_4$, filtered and concentrated in vacuo (85%).

1H-NMR

IS-MS, m/e 354.2 (M+1)

Analysis for $C_{20}H_{23}N_3O_3 \cdot 0.2H_2O$:

Calcd: C, 67.28; H, 6.61; N, 11.77;

Found: C, 67.10; H, 6.46; N, 11.63.

1-(Cbz-D-phenylglycinyl)-4-(1-methylpiperidin-4-yl)piperazine.

Prepared from (Cbz-D-phenylglycinyl)piperazine and 1-methylpiperidin-4-one using Method I-A (but using $NaBH(OAc)_3$ in 1,2-dichloroethane)(49%).

1H-NMR

IS-MS, m/e 451.3 (M+1)

Analysis for $C_{26}H_{34}N_4O_3$:

Calcd: C, 69.31; H, 7.61; N, 12.43;

Found: C, 69.36; H, 7.71; N, 13.14.

1-D-Phenylglycinyl-4-(1-methylpiperidin-4-yl)piperazine dihydrochloride.

To a stirring suspension of 5% Pd/C (0.6 g) in ethanol (25 mL) under nitrogen was added a solution of 1-(Cbz-D-phenylglycinyl)-4-(1-methylpiperidin-4-yl)piperazine (2.6 g, 5.77 mmol) and acetic acid (1.6 mL) in ethanol (50 mL). The flask was placed under vacuum and the atmosphere was replaced with hydrogen (balloon). After 4 h, diatomaceous earth was added and the mixture was filtered through a pad of diatomaceous earth and concentrated in vacuo. The residue was dissolved in ethyl acetate and HCl gas was bubbled through the stirring solution to precipitate the dihydrochloride salt. The mixture was filtered and the solid was dried in vacuo to give 2.6 g (quantitative) of the title compound.

1H-NMR

IS-MS, m/e 317.3 (M+1)

General Procedure: The product of Examples 47-50 was prepared from 1-(D-phenylglycinyl)-4-(1-methylpiperidin-4-yl)piperazine dihydrochloride and the indicated acid using Method I-C (with EDCI in place of DCC).

Example 47

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(1-methylpiperidin-4-yl)piperazine.

Prepared from 4-methoxybenzoic acid (19%).

1H-NMR

IS-MS, m/e 451.0 (M+1)

Analytical RPHPLC, Method A, RT = 16.76 min (100%)

Example 47a

1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(1-methylpiperidin-4-yl)piperazine Dihydrochloride.

Prepared from 1-(4-methoxybenzoyl-D-phenylglycinyl)-4-(1-methylpiperidin-4-yl)piperazine using Method I-D (but using dichloromethane as the initial solvent).

1H NMR

Analysis for $C_{28}H_{28}ClN_5O_2 \cdot 2.0HCl \cdot 0.5H_2O$:

Calcd: C, 58.64; H, 7.00; N, 10.22;

Found: C, 58.92; H, 6.79; N, 10.19.

HPLC Analysis (Method A): 100% t_r = 17.14 min.

Example 48

1-(Indole-6-carbonyl-D-phenylglycinyl)-4-(1-methylpiperidin-4-yl)piperazine.

Prepared from indole-6-carboxylic acid (65%).

1H-NMR

IS-MS, m/e 460.2 (M+1)

Analytical RPHPLC, Method A, RT = 16.68 min (100%)

Example 48a

1-(Indole-6-carbonyl-D-phenylglycinyl)-4-(1-methylpiperidin-4-yl)piperazine Dihydrochloride.

May be prepared from 1-(indole-6-carbonyl-D-phenylglycinyl)-4-(1-methylpiperidin-4-yl)piperazine using Method I-D (but using dichloromethane as the initial solvent).

Example 49

1-(3-Methylindole-6-carbonyl-D-phenylglycinyl)-4-(1-methylpiperidin-4-yl)piperazine.

Prepared from 3-methylindole-6-carboxylic acid (50%).

1H-NMR

IS-MS, m/e 474.3 (M+1)

Analytical RPHPLC, Method A, RT = 22.20 min (98%)

Example 50

1-(3-Chloroindole-6-carbonyl-D-phenylglycinyl)-4-(1-methylpiperidin-4-yl)piperazine.

Prepared from 3-chloroindole-6-carboxylic acid (76%).

1H-NMR

IS-MS, m/e 493.9 (M+1)

Analytical RPHPLC, Method A, RT = 22.66 min (100%)

Example 51

1-(3-Chloroindole-6-carbonyl-D-phenylglycinyl)-4-(4-piperidinylmethyl)piperazine Dihydrochloride.

Preparation of Starting Materials:

1-(1-Boc-piperidin-4-ylmethyl)piperazine.

To a stirring solution of 1-Boc-piperidine-4-carboxaldehyde (2.4 g, 11.3 mmol) in THF (60 mL) and acetonitrile (15 mL) was added piperazine (4.85 g, 56.3 mmol).

After stirring for 5 h, sodium triacetoxyborohydride (2.87 g, 13.5 mmol) was added and the reaction was allowed to stir overnight. The next morning, the solvents were removed by rotary evaporation and the residue was dissolved in ethyl acetate, washed twice with satd aq. $NaHCO_3$, followed by water, then dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was then chromatographed over silica gel, eluting with a step gradient of 2% through 15% (2 N ammonia/methanol) in dichloromethane. The product containing fractions were combined and concentrated in vacuo to give 4.03 g (48%) of the title compound.

1H-NMR

IS-MS, m/e 284.3 (M+1)

1-(Cbz-D-Phenylglycinyl)-4-(1-Boc-piperidin-4-ylmethyl)-piperazine.

Prepared from Cbz-D-phenylglycine and 1-(1-Boc-piperidin-4-ylmethyl)piperazine using Method C-A. The title compound was purified by chromatography over silica gel, eluting with a step gradient of 1% to 3% (2 N ammonia/methanol in dichloromethane.

1H-NMR

IS-MS, m/e 551.3 (M+1)

1-(D-Phenylglycinyl)-4-(1-Boc-piperidin-4-ylmethyl)piperazine.

Prepared from 1-(Cbz-D-phenylglycinyl)-4-(1-Boc-piperidin-4-ylmethyl)piperazine using Method F-A.

1H-NMR

IS-MS, m/e 417.8 (M+1)

1-(3-Chloroindole-6-carbonyl-D-phenylglycinyl)-4-(4-piperidinylmethyl)piperazine Dihydrochloride.

Prepared from 3-chloroindole-6-carboxylic acid and 1-(D-phenylglycinyl)-4-(1-Boc-piperidin-4-ylmethyl)piperazine using Methods I-C, D-B, and I-D (using dichloromethane in place of ether/dichloromethane as an initial solvent).

1H-NMR

IS-MS, m/e 494.2 (M+1)

Analysis for $C_{27}H_{32}N_5O_2Cl \cdot 2.2HCl \cdot 3.0H_2O$:

Calcd: C, 51.61; H, 6.45; N, 11.15; Cl, 18.06;

Found: C, 51.40; H, 6.12; N, 11.02; Cl, 17.80.

Analytical RPHPLC, Method A, RT = 20.59 min (100%)

Example 52

1-(3-Methylindole-6-carbonyl-D-phenylglycinyl)-4-(4-piperidinylmethyl)piperazine Dihydrochloride.

Prepared from 3-methylindole-6-carboxylic acid and 1-(D-phenylglycinyl)-4-(1-Boc-piperidin-4-ylmethyl)piperazine using Methods I-C, D-B, and I-D (using dichloromethane in place of ether/dichloromethane as an initial solvent).

1H-NMR

IS-MS, m/e 474.2 (M+1)

Analysis for $C_{28}H_{35}N_5O_2 \cdot 2.3HCl \cdot 4.0H_2O$:

Calcd: C, 53.42; H, 7.25; N, 11.13; Cl, 12.95;

Found: C, 53.14; H, 6.71; N, 10.99; Cl, 13.12.

Analytical RPHPLC, Method A, RT = 20.23 min (100 %)

Example 53

1-[4-Chlorobenzoyl-D-phenylglycinyl]-4-benzylpiperazine trifluoroacetate.

Boc-D-phenylglycine (753 mg, 3 mmol), TBTU (2-(1H-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate) (963.3 mg, 3 mmol), diisopropylethylamine (894 mg, 6 mmol) and 4-benzylpiperazine (525 mg, 3 mmol) were combined in DMF (10 mL) and stirred overnight. The reaction mixture was taken into dichloromethane (25 mL) washed with water (50 mL) and evaporated to dryness.

The residue was treated with TFA (5 mL) for 1 h and the excess TFA evaporated *in vacuo*. Triethylamine (1 mL) was added and evaporated *in vacuo*. This mixture was then divided into three equal parts. One part was then treated with a mixture of 4-chlorobenzoic acid (156.5 mg, 1 mmol), HOBt (148.5 mg, 1.1 mmol) and EDCI (191 mg, 1 mmol) in DMF (3 mL) that had been stirred for 5 min. The reaction mixture was

stirred overnight, diluted with water and acetonitile, and applied directly for purification by preparative RPHPLC to give the title compound, (120 mg).
1H-NMR

By similar methods to those described in Example 53 the following compounds were prepared:

Example 54
1-[4-Chlorobenzoyl-D-phenylglycinyl]-4-(2-phenethyl)piperazine Trifluoroacetate.

1H-NMR
MS MALDI-TOF M+1 = 462

Example 55
1-[4-Chlorobenzoyl-D-phenylglycinyl]-4-(cyclohexylmethyl)-piperazine Trifluoroacetate.

1H-NMR
MS MALDI-TOF M+1 = 454

The following compounds are prepared using similar procedures to those described above and the appropriate starting materials:

1-[Indole-6-carbonyl-D-phenylglycinyl]-4-[2-(thiazol-2-yl)-ethyl]piperazine.

1-[Indole-6-carbonyl-D-phenylglycinyl]-4-[2-(2-aminothiazol-4-yl)ethyl]piperazine.

1-[Indole-6-carbonyl-D-phenylglycinyl]-4-[2-(3-fluoropyridin-4-yl)ethyl]piperazine.

1-[Indole-6-carbonyl-D-phenylglycinyl]-4-[2-(2-cyanopyridin-4-yl)ethyl]piperazine.

1-[Indole-6-carbonyl-D-phenylglycinyl]-4-[2-(2-methylpyridin-4-yl)ethyl]piperazine.

1-[Indole-6-carbonyl-D-phenylglycinyl]-4-[2-(2-trifluoromethylpyridin-6-yl)ethyl]piperazine.

1-[Indole-6-carbonyl-D-(2-chlorophenyl)glycinyl]-4-[2-(pyridin-4-yl)ethyl]piperazine.

1-[Indole-6-carbonyl-D-(2-chlorophenyl)glycinyl]-4-[2-(pyridazin-3-yl)ethyl]piperazine.

1-[Indole-6-carbonyl-D-(2-chlorophenyl)glycinyl]-4-[2-(imidazol-1-yl)ethyl]piperazine.

1-[Indole-6-carbonyl-D-(2-chlorophenyl)glycinyl]-4-[2-(imidazol-4-yl)ethyl]piperazine.

1-[Indole-6-carbonyl-D-(2-chlorophenyl)glycinyl]-4-[2-(pyrazol-4-yl)ethyl]piperazine.

1-[4-Methoxybenzoyl-D-(2-chlorophenyl)glycinyl]-4-(1-methylpiperidin-4-yl)piperazine.

1-[Indole-6-carbonyl-D-(2-chlorophenyl)glycinyl]-4-(1-methylpiperidin-4-yl)piperazine.

1-[4-Methoxybenzoyl-D,L-(quinolin-8-yl)glycinyl]-4-(1-methylpiperidin-4-yl)piperazine.

1-[Indole-6-carbonyl-D,L-(quinolin-8-yl)glycinyl]-4-(1-methylpiperidin-4-yl)piperazine.

Assay protocols

Enzyme Inhibition assays:

The ability of a test compound to inhibit factor Xa may be evaluated in one or more of the following Enzyme Inhibition assays, or in other standard assays known to those skilled in the art.

Enzyme Inhibition Assay 1

Enzyme assays were carried out at room temperature in 0.1M phosphate buffer, pH7.4 according to the method of Tapparelli et al (J. Biol. Chem. 1993,268,4734-4741). Purified human factor Xa, trypsin, thrombin and plasmin were purchased from Alexis Corporation, Nottingham, UK. Urokinase was purchased from Calbiochem, Nottingham, UK. Chromogenic substrates for these enzymes; pefachrome-FXA, pefachrome-TRY, pefachrome-TH, pefachrome-PL and pefachrome-UK were purchased from Pentapharm AG, Basel, Switzerland. Product (*p*-nitroaniline) was quantified by adsorption at 405nm in 96 well microplates using a Dynatech MR5000 reader (Dynex Ltd, Billingshurst, UK). Km and Ki were calculated using SAS PROC NLIN (SAS Institute, Cary, NC, USA, Release 6.11) K_m values were determined as 100.9μM for factor Xa/pefachrome-FXA and 81.6μM for trypsin/pefachrome-TRY. Inhibitor stock solutions were prepared at 40mM in Me2SO and tested at 500μM, 50μM and 5μM. Accuracy of Ki measurements was confirmed by comparison with Ki values of known inhibitors of factor Xa and trypsin.

In agreement with published data, benzamidine inhibited factor Xa, trypsin, thrombin, plasmin and urokinase with Ki values of 155μM, 21μM, 330nM, 200nM and 100nM respectively. NAPAP

inhibited thrombin with a Ki value of 3nM. Compounds of the invention were found to have activity in these assays.

Enzyme Inhibition Assay 2

Human factor Xa and human thrombin were purchased from Enzyme Research Laboratories (South Bend, Indiana, USA). Other proteases were from other commercial sources. Chromogenic para-nitroanilide peptide protease substrates were purchased from Midwest Biotech (Fishers, Indiana, USA).

The binding affinities for human factor Xa were measured as apparent association constants (Kass) derived from protease inhibition kinetics as described previously.[a,b,c,d] The apparent Kass values were obtained using automated (BioMek-1000) dilutions of inhibitors (Kass determinations are performed in triplicate at each of four-eight inhibitor concentrations) into 96-well plates and chromogenic substrate hydrolysis rates determined at 405 nm using a Thermomax plate reader from Molecular Devices (San Francisco). For factor Xa inhibition, the assay protocol was: 50 µl buffer (0.06 M tris, 0.3 M NaCl, pH 7.4); 25 µl inhibitor test solution (in MeOH); 25 µl human factor Xa (32 nM in 0.03 M tris, 0.15 M NaCl, 1 mg/ml HSA); finally, 150 µl BzIleGluGlyArgpNA (0.3 mM in water) added within 2 min to start hydrolysis. Final factor Xa was 3.2 nM. Free [Xa] and bound [Xa] were determined from linear standard curves on the same plate by use of SoftmaxPro software for each inhibitor concentration and apparent Kass calculated for each inhibitor concentration which produced hydrolysis inhibition between 20% and 80% of the control (3.2 nM factor Xa): apparent Kass $= [E:I]/[E_f][I_f] = [E_b]/[E_f][I^o-I_b]$. The apparent Kass values so obtained are approximately the inverse of the Ki for the respective inhibitors [1/appKass = app Ki]. The variability of mean apparent Kass values determined at the single substrate concentration was +/- 15%. The assay system Km was measured

as 0.347 +/- 0.031 mM [n=4]; and Vmax was 13.11 +/- 0.76 μM/min.

Kass values were determined with thrombin and other proteases using the same protocol with the following enzyme and substrate concentrations: thrombin 5.9 nM with 0.2 mM BzPheValArgpNA; XIa 1.2 nM with 0.4 mM pyroGluProArgpNA; XIIa 10 nM with 0.2 mM HDProPheArgpNA; plasmin 3.4 nM with 0.5 mM HDValLeuLyspNA; nt-PA 1.2 nM with 0.8 mM HDIleProArgpNA; and urokinase 0.4 nM with 0.4 mM pyroGluGlyArgpNA; aPC 3 nM with 0.174 mM pyroGluProArgpNA; plasma kallikrein 1.9 nM with D-ProPheArgpNA; bovine trypsin 1.4 nM with 0.18 mM BzPheValArgpNA.

Citations

(a) Sall DJ, JA Bastian, SL Briggs, JA Buben, NY Chirgadze, DK Clawson, ML Denny, DD Giera, DS Gifford-Moore, RW Harper, KL Hauser, VJ Klimkowski, TJ Kohn, H-S Lin, JR McCowan, AD Palkowitz, GF Smith, ME Richett, K Takeuchi, KJ Thrasher, JM Tinsley, BG Utterback, S-CB Yan, M Zhang. Dibasic Benzo[b]thiophenes Derivatives as a Novel Class of Active Site Directed Thrombin Inhibitors. 1. Determination of the Serine Protease Selectivity, Structure-Activity Relationships and Binding Orientation. J Med Chem 40 3489-3493 (1997).

(b) Smith GF, TJ Craft, DS Gifford-Moore, WJ Coffman, KD Kurz, E Roberts, RT Shuman, GE Sandusky, ND Jones, N Chirgadze, and CV Jackson. A Family of Arginal Thrombin Inhibitors Related to Efegatran. Sem. Thrombos. Hemost. 22, 173-183 (1996).

(c) Smith GF, DS Gifford-Moore, TJ Craft, N Chirgadze, KJ Ruterbories, TD Lindstrom, JH Satterwhite. Efegatran: A New Cardiovascular Anticoagulant. In New Anticoagulants for the

Cardiovascular Patient. Ed. R Pifarre. Hanley & Belfus, Inc., Philadelphia (1997) pp 265-300.

(d) Sall DJ, JA Bastian, NY Chirgadze, ML Denny, MJ Fisher, DS Gifford-Moore, RW Harper, VJ Klimkowski, TJ Kohn, HS Lin, JR McCowan, ME Richett, GF Smith, K Takeuchi, JE Toth, M Zhang. Diamino Benzo[b]thiophene Derivatives as a Novel Class of Active Site Directed Thrombin Inhibitors: 5. Potency, Efficacy and Pharmacokinetic Properties of Modified C-3 Side Chain Derivatives. In press, J Med Chem (1999).

In general, the compounds of formula (I) exemplified herein have been found to exhibit a Ki of 10 μM or less in Assay 1 and/or a Kass of at least 0.1 x 10^6 L/mole in Assay 2.

The ability of a test compound to elongate Partial Thromboplastin Time (Prothrombin Time) may be evaluated in the following test protocols.

Partial Thromboplastin Time (Prothrombin) Test Protocol

Venous blood was collected into 3.2% (0.109m) trisodium citrate vacutainer tubes at 1 volume of anticoagulant to nine volumes of blood. The blood cells were separated by centrifugation at 700g for ten minutes to yield plasma, which was frozen at $70^{O}C$ until required.
To perform the test, 100μl of plasma was pipetted into in a glass test tube, 1μl of test compound in DMSO was added, and allowed to warm to 37^{O} over two minutes. 100μl of warm (37^{O}) Manchester (tissue thromboplasin) reagent (Helena Biosciences, UK) was added, allowed to equilibrate for two minutes. 100μl of warm (37^{O}) 25mM calcium chloride solution was added to initiate clotting. The test tube was tilted three times through a 90^{O} angle every five seconds to mix the reagents and the time to clot formation recorded. Data from a series of

observations and test compound concentrations are analysed by a SAS statistical analysis program and a CT2 (Concentration required to double clotting time) for each compound is generated.

Compounds of the invention were found to significantly elongate the partial thromboplastin time (Prothrombin time).

Alternative Prothrombin Time and APTT Protocols

Coagulation Determinations. Prothrombin Times and APTT values were determined in HUMAN PLASMA with a STA instrument (Stago). BioPT is a special non-plasma clotting assay triggered with human tissue factor (Innovin). Possible binding to albumen or to lipid was assessed by comparing the BioPT effects in the presence/absence of 30 mg/ml human albumen (HSA) and 1 mg/ml phosphatidyl choline (PC). Inhibitors were delivered in 50% MeOH vehicle.

APTT ASSAY

75 µl plasma Citrol *Baxter-Dade* Citrated Normal Human Plasma

25 µl test sol'n

75 µl Actin *Baxter-Dade* Activated Cephaloplastin incubate 2 min min. @ 37°

75 µl $CaCl_2$ (0.02 M)

PT ASSAY

75 µl plasma

25 µl test sol'n

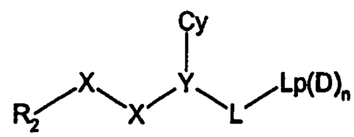
75 µl saline incubate 1 min. @ 37° C

75 µl Innovin *Baxter-Dade* Recombinant Human Tissue Factor

Compounds of the invention were found to be potent inhibitors of factor Xa.

Claims

1. A serine protease inhibitor compound of formula (I)



(I)

wherein:

R_2 is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or R_1, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R_2 cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_{1a} independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R_1 is as defined for R_{1a}, provided that R_1 is not unsubstituted aminoalkyl;

Y (the α-atom) is a nitrogen atom or a CR_{1b} group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, optionally substituted by groups

R_{3a} or $R_{3i}X_i$;

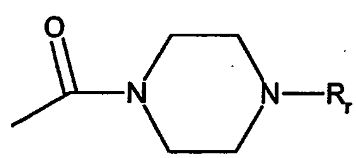
each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkyloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S; and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group), or $-OCH_2O-$ which is bonded to two adjacent ring atoms in Cy;

X_i is a bond, O, NH or CH_2;

R_{3i} is phenyl, pyridyl or pyrimidinyl optionally substituted by R_{3a};

R_{1b}, R_{1c} and R_{1j} are as defined for R_{1a}; and

$-L-Lp(D)_n$ is of the formula:



in which R_r is $-(CH_2)_c-R_c$, $-CHR_eR_f$, $-CH_2-CHR_eR_f$, $-CH_2-CH_2-CHR_eR_f$, or R_g in which c is 1 or 2; R_c is thienyl, thiazolyl (which may bear an amino substituent), isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridyl (which may bear an alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, (1-4C)alkoxycarbonyl, carboxy, acetylamino, chloro, fluoro, cyano, (1-3C)alkyl, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl or tetrazolyl substituent), pyrimidinyl, pyridazinyl, pyrazinyl or phenyl (which may bear a methyl, methylamino, dimethylamino, carboxy, dialkylaminosulphonyl, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, alkoxycarbonyl, acetylamino, chloro, fluoro, cyano, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl or tetrazolyl substituent); each of R_e and R_f independently is hydrogen or C_{1-3}alkyl; or CHR_eR_f is cyclopentyl (which may

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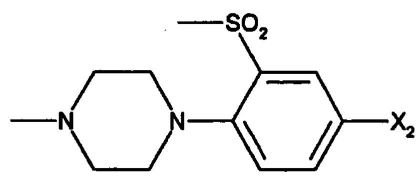
bear a hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl substituent at the 3- or 4-position), cyclohexyl (which may bear a hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl substituent at the 3- or 4-position), tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, pyrrolidin-3-yl (which may bear a hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl substituent at the 1-position), piperidin-4-yl (which may bear a hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl substituent at the 1-position), or indan-2-yl; and R_g is 2-methylsulphonylphenyl which may bear a 4-fluoro substituent or R_g is λ^6-1,1-dioxobenzo[b]thiophen-7-yl;

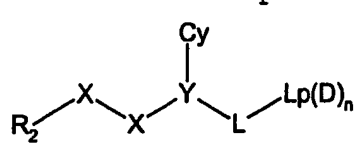
or a physiologically-tolerable salt thereof; provided that Lp(D)n is not of the formula (K):



(K)

wherein X_2 is fluoro or hydrogen.

2. A serine protease inhibitor compound of formula (I)



(I)

wherein:

R_2 is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or

difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or R_1, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R_2 cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_{1a} independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R_1 is as defined for R_{1a}, provided that R_1 is not unsubstituted aminoalkyl;

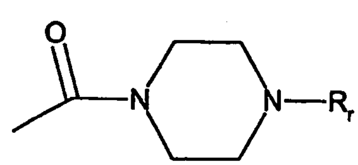
Y (the α-atom) is a nitrogen atom or a CR_{1b} group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, optionally substituted by groups R_{3a} or phenyl optionally substituted by R_{3a};

each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl;

R_{1b}, R_{1c} and R_{1j} are as defined for R_{1a}; and

-L-Lp(D)$_n$ is of the formula:

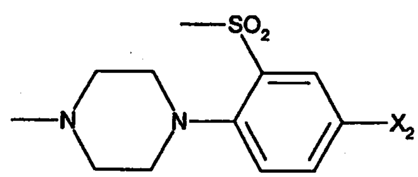


in which R_r is $-(CH_2)_c-R_c$, $-CHR_eR_f$, $-CH_2-CHR_eR_f$, or R_g in which c is 1 or 2; R_c is pyridyl or phenyl (which phenyl may

bear a fluoro, chloro, methyl, $CONH_2$, SO_2NH_2, methylaminosulphonyl, dimethylaminosulphonyl, methoxy or methylsulphonyl substituent); each of R_e and R_f independently is hydrogen or C_{1-3}alkyl; or CHR_eR_f is cyclopentyl (which may bear a methyl, ethyl or hydroxymethyl substituent at the 3- or 4-position), cyclohexyl (which may bear a methyl, ethyl or hydroxymethyl, (1-3C)alkyl, carboxy, methoxycarbonyl or ethoxycarbonyl substituent at the 3- or 4-position), tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, pyrrolidin-3-yl (which may bear a 1-methyl substituent), or indan-2-yl; and R_g is 2-methylsulphonylphenyl which may bear a 4-fluoro substituent or R_g is λ^6-1,1-dioxobenzo[b]thiophen-7-yl;

or a physiologically-tolerable salt thereof;

provided that Lp(D)n is not of the formula (K):



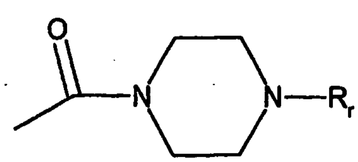
(K)

wherein X_2 is fluoro or hydrogen.

3. A compound according to claim 1 or claim 2 wherein R_r is of the formula $-(CH_2)_c-R_c$.

4. A compound according to any one of claims 1 to 3 wherein c is 2.

5. A compound according to claim 1 wherein $-L-Lp(D)_n$ is of the formula:



in which R_r is $-(CH_2)_c-R_c$; in which c is 2; R_c is thienyl, thiazolyl (which may bear an amino substituent), isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl,

pyridyl (which may bear an amino, methoxycarbonyl, carboxy, fluoro, cyano, methyl, methylsulphonyl, aminosulphonyl, methylaminosulfonyl, dimethylaminosulfonyl, or trifluoromethyl substituent), pyrimidinyl, pyridazinyl, pyrazinyl or phenyl (which phenyl may bear a fluoro, chloro, cyano, methyl, amino, methylsulphonyl, aminosulphonyl, methylaminosulphonyl, dimethylaminosulphonyl, methylamino, dimethylamino, carboxy, methoxycarbonyl or methoxy substituent).

6. A compound according to any one of claims 1 to 5 wherein Rc is thiazolyl (which may bear an amino substituent), pyrimidinyl, pyrazolyl, imidazolyl, pyridyl (which may bear a methylsulphonyl, aminosulphonyl, methylaminosulfonyl, dimethylaminosulfonyl, fluoro, cyano, methyl or trifluoromethyl substituent), pyridazinyl, pyrazinyl or phenyl (which phenyl may bear a fluoro, chloro, cyano, methyl, amino, methylamino, dimethylamino, carboxy, methoxycarbonyl, methylsulphonyl, aminosulphonyl, methylaminosulfonyl, dimethylaminosulfonyl, or methoxy substituent).

7. A compound according to any one of claims 1 to 5 wherein Rc is thiazolyl (which may bear an amino substituent), pyrazolyl, imidazolyl, pyridyl (which may bear a fluoro, cyano, methyl or trifluoromethyl substituent), pyridazinyl or pyrazinyl.

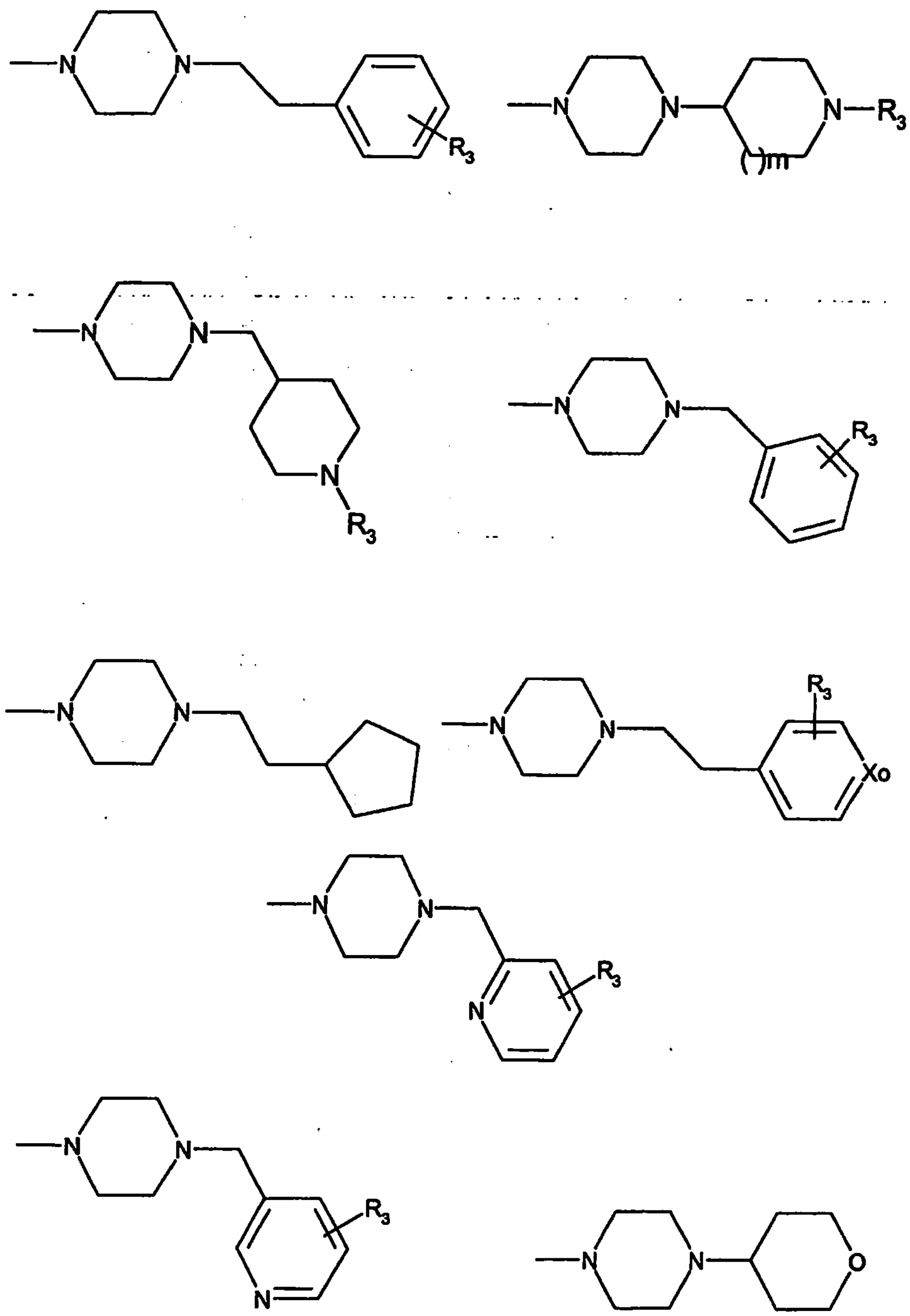
8. A compound according to any one of claims 1 to 5 wherein Rc is thiazol-2-yl, 2-aminothiazol-4-yl, pyrazol-1-yl, pyrazol-4-yl, pyridazin-3-yl, imidazol-1-yl, imidazol-4-yl, pyrazin-2-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 3-fluoropyrid-4-yl, 2-cyanopyrid-4-yl, 2-methylpyrid-4-yl or 2-trifluoromethylpyrid-6-yl.

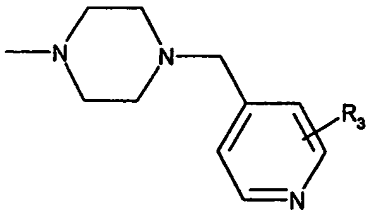
9. A compound according to any one of claims 1 to 5 wherein Rc is pyrazolyl, imidazolyl, pyridyl, pyridazinyl or pyrazinyl.

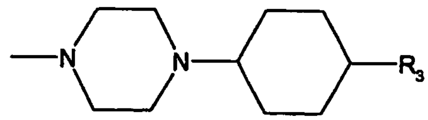
10. A compound according to any one of claims 1 to 5 wherein

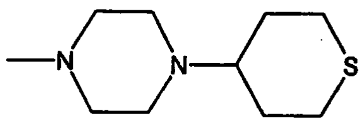
Rc is pyrid-2-yl, pyrid-3-yl or pyrid-4-yl.

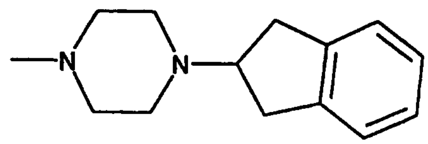
11. A compound according to claim 1 wherein -Lp(D)n is of the formula:

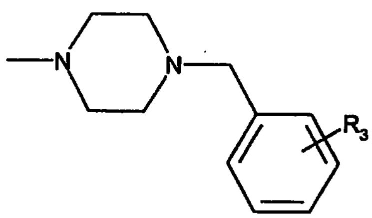


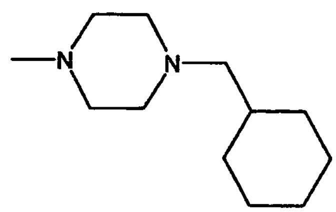


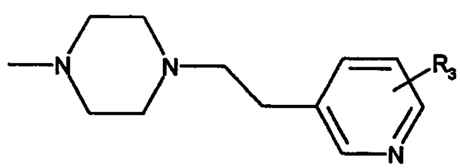


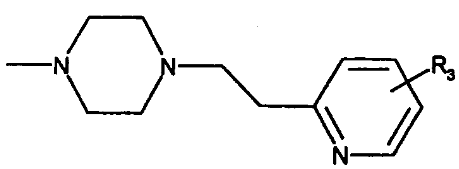


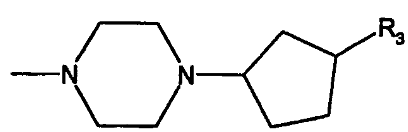












wherein;

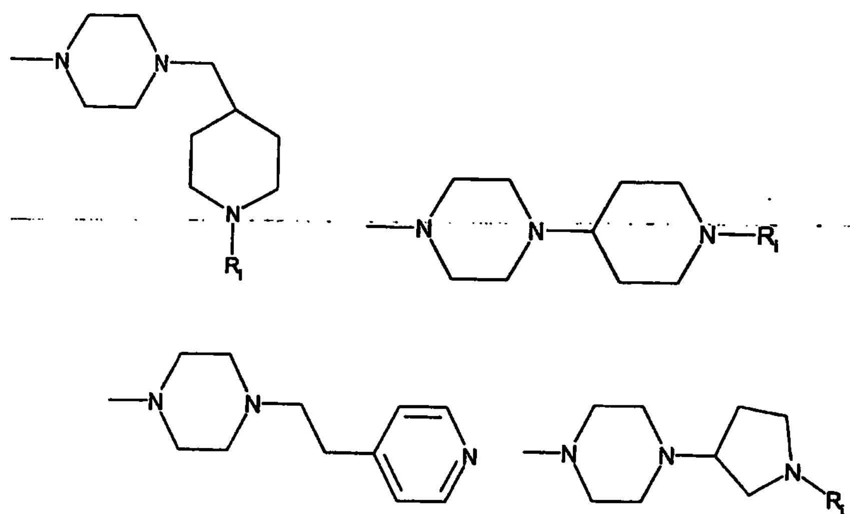
m represents 0 or 1;

X^0 represents CH or N; and

when R_3 is present as a substituent on an aromatic ring, it is selected from hydrogen, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, alkoxycarbonyl, acetylamino, chloro, fluoro, cyano, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl and tetrazolyl; and

when R_3 is present as a substituent on a saturated ring, it is selected from hydrogen, hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl and ethoxycarbonyl.

12. A compound according to claim 11 wherein -Lp(D)n is of the formula:



wherein R_1 is hydrogen or (1-6C)alkyl.

13. A compound according to any one of claims 1 to 12 wherein the 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, in R_2, is selected from phenyl, pyrrolyl, pyridyl, pyrazinyl, furyl and thienyl (optionally substituted as defined in claim 1).

14. A compound according to any one of claims 1 to 12 wherein R_2 is phenyl (optionally substituted as defined in claim 1).

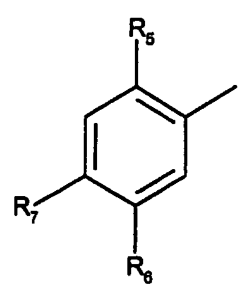
15. A compound according to any one of claims 1 to 12 wherein R_2 is naphthyl, benzimidazolyl, isoquinolinyl, indolyl, indazolyl, 3,4-methylenedioxyphenyl, dihydroindolyl, benzothiazolyl, benzo[b]thiophenyl, benzofuryl, imidazo[1,2-a]pyrimidinyl, tetrahydroimidazo[1,2-a]pyrimidinyl or benzisoxazolyl (each of which is optionally substituted as defined in claim 1).

16. A compound according to any one of claims 1 to 12 wherein R_2 is phenyl, thien-2-yl, naphthyl, indol-2-yl, indol-6-yl, benzo[b]furan-5-yl, benzo[b]thiophen-2-yl or benzimidazol-2-yl (each of which is optionally substituted as defined in claim 1).

17. A compound according to any one of claims 1 to 16 wherein optional substituents for R_2 are selected from: fluoro, chloro, bromo, iodo, nitro, thiol, difluoromethoxy, trifluoromethoxy, hydrazido, methylhydrazido, amino, cyano, trifluoromethyl, methylthio, vinyl, ethynyl, acetylamino, carboxy, acetoxy, hydroxy, methyl, ethyl, amido ($CONH_2$), aminomethyl, methoxy and ethoxy.

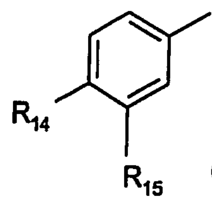
18. A compound according to any one of claims 1 to 16 wherein R_2 is optionally substituted by 1 or 2 substituents selected from fluoro, chloro, amino, methyl, ethyl and methoxy.

19. A compound according to any one of claims 1 to 12 wherein R_2 is of the formula:

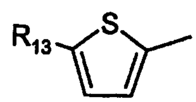


in which R_5 is amino, hydroxy or hydrogen, and R_6 and R_7, which may be the same or different, are halo, nitro, thiol, cyano, haloalkyl, haloalkoxy, amido, hydrazido, amino, alkylthio, alkenyl, alkynyl or R_1 (as defined in claim 1) or taken together form a 5 or 6 membered fused carbocyclic ring or 5 membered heterocyclic ring, which may itself be substituted by R_{1j} (as defined in claim 1), amino, halo, cyano, nitro, thiol, alkylthio, haloalkyl or haloalkoxy.

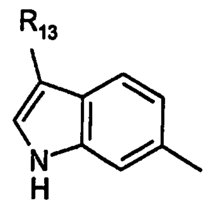
20. A compound according to any one of claims 1 to 12 wherein R_2 is selected from one of the formula (A') to (H'):



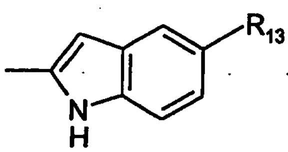
(A')



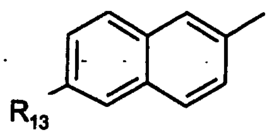
(B')



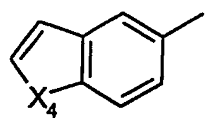
(C')



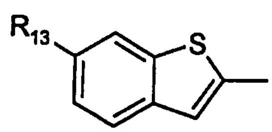
(D')



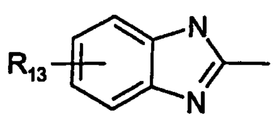
(E')



(F')



(G')



(H')

wherein X_4 is O or S, R_{13} is selected from hydrogen, fluoro, [except for (C')] chloro or methyl and R_{14} is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and R_{15} is selected from hydrogen, methyl, fluoro, chloro and amino.

21. A compound according to claim 20, wherein R_2 is of the formula (A') (wherein R_{14} is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and R_{15} is selected from hydrogen, methyl, fluoro, chloro and amino) or of the formula (B') (wherein R_{13} is chloro) or of the formula (C') (wherein R_{13} is selected from hydrogen, methyl and chloro) or of the

formula (D') (wherein R_{13} is selected from hydrogen, methyl, fluoro and chloro) or of the formula (E') (wherein R_{13} is hydrogen) or of the formula (G') (wherein R_{13} is chloro).

22. A compound according to claims 1 to 12, wherein R_2 is 4-chlorophenyl, 4-methoxyphenyl, 3-amino-4-chlorophenyl, indol-2-yl, 5-chloroindol-2-yl, indol-6-yl, 3-chloroindol-6-yl or 3-methylindol-6-yl.

23. A compound according to claim 20 wherein R_2 is of the formula (A') or (C') and R_{13}, R_{14} and R_{15} are as defined in claim 20.

24. A compound according to claim 20 wherein R_2 is of the formula (A') and R_{14} is methoxy and R_{15} is hydrogen/or of the formula (C') and R_{13} is hydrogen, methyl or chloro.

25. A compound according to any one of claims 1 to 24 wherein -X-X- is selected from -CH=CH-, -CONH-, -CONR_{1a}-, -NH-CO-, -NH-CH_2-, -CH_2-NH-, -CH_2O-, -OCH_2-, -COO-, -OC=O- and -CH_2CH_2- wherein R_{1a} is as defined in claim 1.

26. A compound according to any one of claims 1 to 24 wherein -X-X- is -CONH-.

27. A compound according to any one of claims 1 to 26 wherein R_{1b} is hydrogen, methyl or hydroxymethyl.

28. A compound according to any one of claims 1 to 26 wherein R_{1b} is hydrogen.

29. A compound according to any one of claims 1 to 26 wherein Y is CH.

30. A compound according to any one of claims 1 to 29 wherein Cy is an optionally R_{3a} substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl, furanyl, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, imidazolyl,

1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrimidinyl, pyridazinyl, quinolyl, isoquinolyl, benzofuryl, benzothienyl or cycloalkyl group, or a phenyl group substituted by $R_{3i}X_i$ in which X_i is a bond, O, NH or CH_2 and R_{3i} is phenyl, pyridyl or pyrimidyl optionally substituted by R_{3a}.

31. A compound according to any one of claims 1 to 29 wherein Cy is an optionally R_{3a} substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl or cycloalkyl group.

32. A compound according to any one of claims 1 to 31 wherein R_{3a} is selected from hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), amino, halo, cyano, nitro,thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S; and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group) and $-OCH_2O-$ which is bonded to two adjacent ring atoms in Cy.

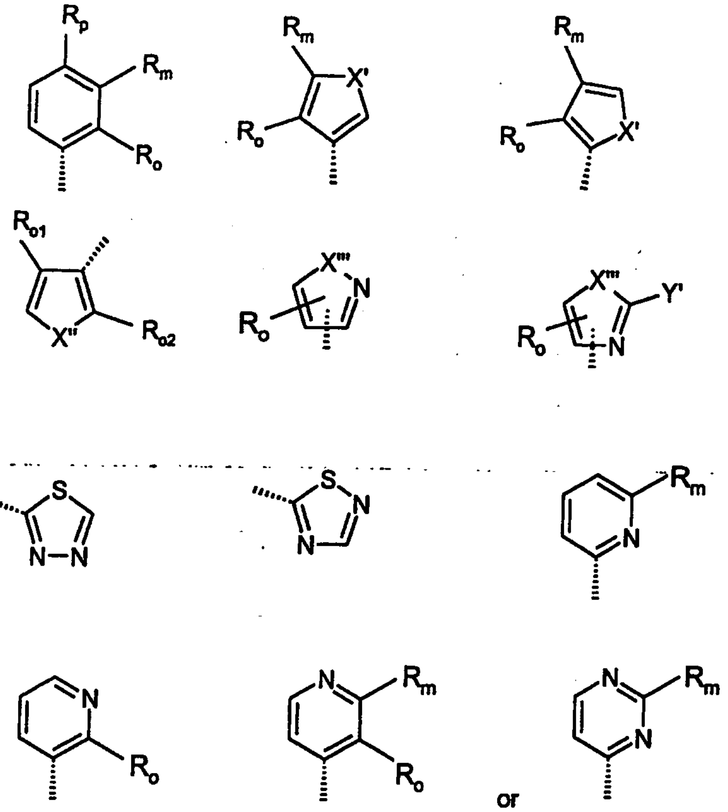
33. A compound according to any one of claims 1 to 31 wherein R_{3a} is selected from hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), aminoalkyl (substituted by hydroxy, alkylamino, alkoxy, oxo,

aryl or cycloalkyl), amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl.

34. A compound according to any one of claims 1 to 31 wherein R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylamino-carbonyl, aminomethyl, $CONH_2$, CH_2CONH_2, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, bromo, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl, bromo, $-OCH_2O-$ (which is bonded to two adjacent ring atoms in Cy) and $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group).

35. A compound according to any one of claims 1 to 31 wherein R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylamino-carbonyl, aminomethyl, $CONH_2$, CH_2CONH_2, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and trifluoromethyl.

36. A compound according to any one of claims 1 to 29 wherein Cy is selected from:



wherein:

X' is selected from O, S and NMe;

X'' is selected from O and S;

X'" is selected from O, S, NH and NMe;

Y' is selected from hydrogen, amino and methyl;

R_o is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and methylsulphonyl;

R_m is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or

together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);

R_p is selected from hydrogen and fluoro; or R_o and R_m or R_m and R_p form an $-OCH_2O-$ group; or R_o and R_m together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroary ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur);

one of R_{o1} and R_{o2} is hydrogen and the other is R_o;

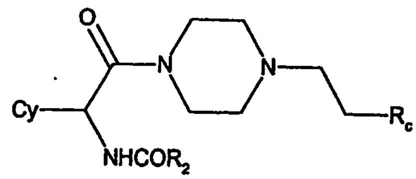
37. A compound according to any one of claims 1 to 29 wherein Cy is selected from phenyl (optionally substituted by methyl, ethyl, prop-2-yl, phenoxy, hydroxy, ethoxy, benzyloxy, prop-2-yloxy, nitro, amino, acetylamino, methylsufonylamino, dimethylamino, chloro, methoxy, trifluoromethyl, methylthio, methylsulfonyl, tert-butylthio, tert-butylsulfonyl, aminosulfonyl or carbamoyl), pyridyl, thienyl, furanyl, imidazolyl, thiazolyl (optionally substituted by amino), napththyl, isoquinolinyl and quinolinyl.

38. A compound according to any one of claims 1 to 29 wherein Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5yl, naphthyl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl, and quinolin-8-yl.

39. A compound according to any one of claims 1 to 29 wherein Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5yl and quinolin-4-yl.

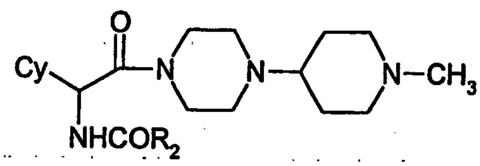
40. A compound according to any one of claims 1 to 29 wherein Cy is selected from phenyl, 2-methoxyphenyl, 4-carbamoylphenyl and pyrid-2-yl.

41. A compound of the formula:



wherein Cy, R_2 and R_c are as defined in any one of claims 1 to 40.

42. A compound of the formula:



wherein Cy and R_2 are as defined in any one of claims 1 - 40.

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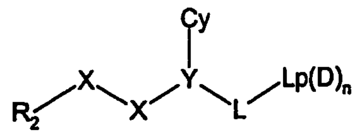
A B S T R A C T

Compounds of formula (I)



(I)

in which R_2, X, Y, Cy, L and $Lp(D)_n$ have the meanings given in the specification, are inhibitors of the serine protease, Factor Xa and are useful in the treatment of cardiovascular disorders.